Dietary Exposure Assessment and Contaminants Biomonitoring in the Dehcho Region, Northwest Territories: Exploring the Relationship Between Mercury Exposure, Omega-3 Fatty Acid Status, and Fish Consumption

by

Matthew Laird

A thesis
presented to the University of Waterloo
in fulfillment of the
thesis requirement for the degree of
Master of Science
in
Public Health and Health Systems

Waterloo, Ontario, Canada, 2017

Author's Declaration

This thesis consists of material all of which I authored or co-authored: see Statement of Contributions included in the thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

Statement of Contributions

This thesis presents the work of Matthew Laird in direct collaboration with his thesis supervisor, Dr. Brian Laird. I would like to acknowledge the contributions made to this research by all co-authors, in addition to my supervisor for providing guidance and insight throughout every stage of the project.

Chapter 4

Chapter 4 of this thesis was co-authored with Juan J. Aristizabal Henao, Dr. Ken D. Stark, George Low, Dr. Heidi K. Swanson, Ellen S. Reyes, and Dr. Brian D. Laird. Juan J. Aristizabal Henao and Dr. Ken Stark completed the lipid extraction and fatty acid analysis of fish tissues from fish harvested in the Dehcho. Dr. Heidi Swanson and George Low designed and implemented the regional mercury monitoring project from which all fish samples were obtained. Dr. Heidi Swanson performed the total mercury analysis for all fish samples, and assisted with the statistical analysis. Dr. Brian Laird provided ongoing guidance and supervision throughout the processes of data collection, study design, and statistical analysis. All authors reviewed the final manuscript, and provided any editorial advice prior to submission for peer-reviewed publication. Ellen Reyes compiled and consolidated the initial dataset based on fish samples harvested in August 2013, spearheaded the design of the initial probabilistic model, and characterized the relationships between omega-3 fatty acids and mercury by species and lake from Year 1 of the study.

Citation: Laird, M.J, Aristizabal Henao, J.J., Reyes, E.S., Stark, K.D., Low, G., Swanson, H.K., and Laird, B.D. (2017). Mercury and Omega-3 Fatty Acid Profiles of Wild-harvested Fish of the

Dehcho Region, Northwest Territories: Contaminant Risks versus Nutrient Value. *Scientific Reports*. (Accepted pending revisions).

Chapter 5

Chapter 5 of this thesis was co-authored with Juan J. Aristizabal Henao, Dr. Ken D. Stark, George Low, Dr. Heidi K. Swanson, Dr. Brian Branfireun, Dr. Mylène Ratelle, and Dr. Brian D. Laird. All co-authors have or are contributing both directly and indirectly to a large, interdisciplinary and multi-institutional research project funded by the Northern Contaminants Program. Juan Jose Aristizabal Henao and Dr. Ken D. Stark completed the lipid extraction and fatty acid analysis of fish tissues harvested from the Dehcho. Dr. Heidi Swanson completed the mercury analyses for fish tissue mercury. Dr. Brian Branfireun and the lab staff at Biotron Analytical Services assisted in the hair mercury analyses. Dr. Brian D. Laird and Dr. Mylène Ratelle were responsible for coordinating the design and implementation of the Contaminant Biomonitoring Study in the Northwest Territories Mackenzie Valley.

Citation: Laird, M.J, Aristizabal Henao, J.J., Stark, K.D., Low, G., Swanson, H.K., Branfireun, B., Ratelle M, and Laird, B.D. (2017). Probabilistic Modeling of Exposure to Mercury in the Dehcho Region of the Mackenzie Valley, Northwest Territories: The Contaminants Biomonitoring Study. *(In Preparation).*

Abstract

Background: Fish are often rich in essential micronutrients including omega-3 fatty acids (FA), and are a cultural and dietary staple in traditional food systems of First Nations communities in the Canadian subarctic. Country foods including fish contribute to improved food security, and promote the cultural sovereignty of First Nations communities. However, these foods are often a primary route of exposure to methylmercury, an environmental contaminant that can pose significant adverse health risks.

Objectives: The objectives of this study are to: 1) Determine the concentration of total mercury (Hg) and long chain omega-3 polyunsaturated fatty acids (omega-3 PUFAs) in the muscle tissue of various wild-caught freshwater fish species harvested from eight lakes in the Dehcho region, Northwest Territories (NWT); 2) Construct a probabilistic, population-based retrospective dose reconstruction model to assess dietary omega-3 PUFA intake and Hg exposure across several Dehcho First Nations communities; 3) Characterize and quantify sources of mercury and omega-3 PUFA exposure from country food consumption, and identify key contributors from the diet; and 4) Assess the utility and accuracy of the probabilistic exposure model at estimating population-level profiles of risk and cardioprotective benefit using biomarkers for omega-3 PUFAs in blood plasma and Hg in hair.

Methods: Samples from eight freshwater fish species [Burbot (*Lota lota*; also known as Loche or Mariah), Cisco (*Coregonus artedi*; also known as Herring), Lake Trout (*Salvelinus namaycush*), Lake Whitefish (*Coregonus clupeaformis*), Longnose Sucker (*Catostomus catostomus*), Northern Pike (*Esox lucius*; known locally as Jackfish), Walleye (*Sander vitreus*; also known as Pickerel) and White Sucker (*Catastomus commersoni*)] were harvested from eight lakes of the Dehcho (including Ekali, Trout, Sanguez, Tathlina, McGill, Gargan, Mustard, and

Kakisa Lakes) in August of 2013, 2014, and 2015. Omega-3 PUFA levels in fish tissue were determined by a lipid extraction on pulverized, homogenized fish tissue and quantified using a gas chromatograph with a flame ionization detector, and freeze-dried, homogenized fish muscle tissue samples were analyzed and quantified for total Hg using a Direct Mercury Analyzer. Fish mercury and fatty acid profiles were paired with primary species-specific country food consumption data collected during the Contaminants Biomonitoring Study in the Northwest Territories Mackenzie Valley using a food frequency questionnaire (FFQ). A retrospective probabilistic dose reconstruction model was developed using Oracle Crystal Ball™ advanced risk modeling software, to simultaneously characterize intake of methylmercury (MeHg) and n-3 PUFAs through country food consumption, and to estimate both the population proportion at risk of exceeding the tolerable daily intake for MeHg, and those not meeting adequate intakes for PUFAs. A two-dimensional Monte Carlo analysis was conducted and profiles of exposure to MeHg and n-3 PUFAs were generated. Results from the model output were compared to toxicological and nutritional data from the results of the Contaminant Biomonitoring Study in the Northwest Territories Mackenzie Valley.

Results: Mean HgT concentrations within piscivorous fishes (e.g. Northern Pike, Walleye, Burbot and Lake Trout) were up to 7.3 times higher than observed in benthivorous and planktivorous fishes (e.g. Cisco, Lake Whitefish, and Sucker). Further, EPA+DHA concentrations in Lake Trout were up to 4.5 times higher than observed in other piscivorous fish species harvested, including Burbot, Northern Pike, and Walleye. Significant differences were noted for mercury and fatty acid profiles in fish between lakes. Negative correlations were observed between mercury and fatty acids for Burbot, Northern Pike and Walleye. Stratifying by species, mean DHA:HgT ratios for Lake Whitefish and Cisco were up to 8.7-fold higher than in

piscivorous fish species including Northern Pike, Walleye and Burbot. As an exception, Lake Trout, demonstrating higher omega-3 PUFAs than other species, had accordingly higher fatty acid:mercury ratios.

Based on fatty acid and mercury levels in fish species of the Dehcho, and results from the FFQ, estimates for mercury exposure from fish consumption among the Dehcho population indicated that up to 7% of trials exceeded the pTWI of 3.29 μg/kg/week (0.47 μg/kg/day). In contrast, only 0.5% of respondents within participating Dehcho communities exceeded Health Canada's recommended guidance value of 6 mg/kg. Mean hair mercury was 0.74 mg/kg, with a geometric mean of 0.38 mg/kg. Generally, only a small proportion of trial values exceeded Dietary Reference Intakes for fatty acid subgroups DHA, EPA+DHA, and total omega-3 PUFAs. Similarly, the Omega-3 Index of participants indicated levels of EPA+DHA that fell within the category associated with very low cardioprotective benefits. Sensitivity analyses indicated that input variables corresponding to Lake Whitefish were strong drivers of fatty acid intake across all fatty acid subgroups, while the proportion of the population consuming Northern Pike and Walleye were primary drivers of exposure to methylmercury intake.

Conclusion: Probabilistic models provide an important lens for characterizing the risks and benefits from country food consumption in First Nations communities of the Dehcho region. Future studies in probabilistic human health risk assessment will incorporate a component to the model that characterizes risk not only within the general population, but in demographics most vulnerable to the risks associated with mercury exposure, including young children, women of childbearing age, and pregnant women. Any consumption notices and advisories that outline recommendations to modify country food use must consider the multitude of sociocultural, nutritional and spiritual benefits of these foods in subarctic Indigenous populations.

Acknowledgements

First of all, I would like to extend my profound thanks to my supervisor, Dr. Brian Laird. Brian was a source of continuing support, guidance and insight throughout this project in both a personal and academic capacity, and his passion for his work and for his students is contagious. He is a thoughtful and compassionate supervisor who continually offered me opportunities to grow, to learn and to develop in this field. For this, I am truly grateful. I would also like to extend my sincere gratitude and thanks to my committee members, Dr. John Mielke, Dr. Glenn Ferguson, and Dr. Heidi Swanson, for their feedback, support and methodological recommendations throughout this project. I would like to thank Sara and Susan for their help in the earlier stages of this work, and Mylene for all of her hard work in putting together and planning the logistics of our work in the Territories, and for her academic, personal and professional advice and support in my work.

I would also like to express my gratitude to the participating First Nations communities of the Dehcho region, for whom this research is dedicated. My experience with First Nations communities in the Canadian subarctic has been unwaveringly positive, and I am immensely grateful, both to my supervisor and to the communities of the Dehcho, for the opportunity to work with so many compassionate and invested people. I would also like to thank Dr. Heidi Swanson and George Low, for designing and implementing the "Return to Country Foods Project".

I would like to acknowledge the funding I received through the School of Public Health and Health Systems at the University of Waterloo. I would also like to thank the support received through funding provided by the Northern Contaminants Program which is jointly funded through Aboriginal Affairs and Northern Development Canada and Health Canada. Further

funding to support this research was obtained through the Natural Sciences and Engineering Research Council of Canada, Health Canada's Climate Change Adaptation Fund, the Cumulative Impacts Monitoring Program, and Polar Knowledge Canada.

Lastly, I would like to thank my friends and family, for their continued support during my graduate studies. I am immeasurably grateful to have such a wonderful group of compassionate, loving and caring people who are always there to provide their unwavering support - I couldn't have done it without you.

Table of Contents

List of Figures

List of Tables

List of Abbreviations

CHMS	Canadian Health Measures Survey
CVD	Cardiovascular Disease
DHA	Docosahexaenoic Acid
DHSS	Department of Health and Social Services
DMA	Direct Mercury Analyzer
DPA	Docosapentaenoic Acid
DRI	Dietary Reference Intake
EDI	Estimated Daily Intake
EFSA	European Food Safety Authority
EPA	Eicosapentaenoic Acid
FAO	Food and Agriculture Organization of the United Nations
FNBI	First Nations Biomonitoring Initiative
FNFNES	First Nations Food, Nutrition and Environment Study
GC	Gas Chromatography
GNWT	Government of the Northwest Territories
IHS	Inuit Health Survey
ISSFAL	International Society for the Study of Fats and Lipids
JECFA	The Joint FAO/WHO Expert Committee on Food Additives
LOD	Level of Detection
NOAEL	No-observed-adverse-effect-level
POD	Point of Departure
PTDI	Provisional Tolerable Daily Intake

PTWI Provisional Tolerable Weekly Intake

PUFA Polyunsaturated fatty acid

RfD Reference Dose

TRV Toxicity Reference Value

WHO World Health Organization

1. Introduction

Mercury is a persistent, toxic global pollutant that affects human and ecosystem health (Driscoll et al., 2013). Mercury is a naturally-occurring element of which natural fluxes occur primarily through the weathering of soil, rocks, and through wildfires and volcanic activity (Health Canada, 2007). However, anthropogenic flux results in the enhanced movement of mercury in the atmosphere, predominantly through industrial processes that include coal combustion, smelting operations and waste incineration (Roman et al., 2011). The fate of Hg in the environment is controlled primarily through long-range atmospheric transport, biogeochemical and food web processes. The environmental cycling of this metal influences the chemical forms it takes, whether present as elemental mercury, inorganic mercury, or organic methylmercury (MeHg) (Wiener et al., 2003).

Subarctic Aboriginal populations are particularly vulnerable to methylmercury exposure (Donaldson et al., 2010; Lemire et al., 2015). Elemental mercury (Hg^0) is converted to its oxidized state, Hg^{2+}, which is converted through microbial methylation into MeHg. Methylmercury biomagnifies in aquatic food chains, and can accumulate to elevated concentrations in higher trophic level predatory fish and marine mammals that are often consumed as components of traditional food systems in subarctic First Nations communities (Receveur et al., 2007).

In contrast to other forms of mercury, methylmercury is absorbed almost completely unhindered through the intestinal epithelium, and can transport readily across the blood-brain barrier and the placental barrier, into fetal circulation (Ralston and Raymond, 2010; Vázquez et al., 2014; Lemire et al., 2015). Extensive toxicological and epidemiological evidence has demonstrated definitive causal links between methylmercury exposure and neurotoxic outcomes,

particularly with *in utero* exposure (e.g., Lam et al., 2013). Characterizing methylmercury exposure is an important component of risk-benefit analyses of country food consumption in subarctic populations, and effective risk assessment and management strategies play an integral role in guiding public health decision-making in this demographic.

Traditional food systems, which include wild-harvested freshwater fish, hold significant cultural, socioeconomic and nutritional value, and are an integral contribution to overall wellbeing in the Dehcho First Nations communities of the Canadian subarctic. Country foods contribute to food security in remote subarctic Indigenous communities, and are important dietary sources of omega-3 fatty acids and other essential micronutrients (e.g., Lemire et al., 2015). Sufficient dietary intake of long-chain omega-3 polyunsaturated fatty acids is suggested to mitigate the health effects of some inflammatory disorders, reduce the risk of certain forms of cardiovascular disease, and contribute to optimal neurocognitive development in early stages of the lifespan (Mozaffarian and Rimm, 2006; Dunstan et al., 2008; Mahaffey et al., 2011; Ruxton, 2011). However, studies suggest that these foods, particularly predatory fish, are also dominant contributors to MeHg exposure in Canadian Indigenous communities (e.g., Mergler et al., 2007).

Effective risk assessment and communication warrants thoughtful consideration of the unique social and cultural specificities that characterize First Nations subpopulations in the Canadian subarctic (Friendship and Furgal, 2012). Due to elevated methylmercury levels found in wild-harvested freshwater fish of the Dehcho, food consumption advisories warning the public of potential contaminant exposure have occasionally been deemed necessary in order to mitigate any associated risks of fish-derived methylmercury exposure (DHSS, 2016). Given the chronic food insecurity affecting many subarctic Indigenous communities, care must be taken to consider potentially negative nutritional outcomes associated with food advisories that warn against the

consumption of these cultural and dietary staples (Chan et al., 1999; Egeland et al., 2011). Risk management strategies and policy development must explicitly consider not only the risks posed by exposure to environmental contaminants, but also the sociocultural, nutritional, economic, and spiritual benefits that are inherent in traditional food systems.

This thesis project investigated and characterized mercury exposure from country foods, particularly from wild-harvested freshwater fish, in communities of the Dehcho region in the Northwest Territories. Firstly, this project collated and analyzed a composite dataset of total mercury and omega-3 fatty acid profiles in the tissues of fish harvested in freshwater lakes of the Mackenzie River Basin in the Dehcho region. With the assistance of Dr. Ken Stark and colleagues at the University of Waterloo, total lipid extraction, followed by separation and analysis using a gas chromatograph with a flame ionization detector, isolated and characterized fatty acid content in each species of fish caught for the purposes of this study. Using a Milestone Direct Mercury Analyzer, Dr. Heidi Swanson and members of her lab team in the Department of Biology at the University of Waterloo measured total mercury content in the muscle tissues of fish harvested from Dehcho lakes in 2013, 2014, and 2015. Using Crystal Ball probabilistic modeling software, the Monte Carlo technique was employed to develop and refine a probabilistic dose reconstruction model that characterized mercury and omega-3 PUFA intake in communities of the Dehcho. This thesis project, and specifically the design of the probabilistic dose reconstruction model described herein, serves as a tool to explore the intersection between the inherent risks and benefits of country foods.

Secondly, this work incorporated a subset of results collected during Years 1 and 2 of the Contaminants Biomonitoring Study, in order to evaluate community profiles of mercury exposure from hair mercury measurements and overall omega-3 PUFA from blood omega-3

PUFAs. A collated mercury and fatty acid dataset from Chapter 4 of this thesis project was paired with hair mercury analyses and dietary survey data collected in five communities of the Dehcho region to generate estimates of mercury and omega-3 intakes. This projects lays the foundation for the assessment of dietary determinants of hair mercury at the population level, and beyond this project the model and method will need to be validated first by assessing the correlation between individual blood and hair mercury, and estimated mercury intake. To achieve this, the study will continue in the Dehcho and a growing sample size will enhance the statistical power and precision of the model in predicting and characterizing individual profiles of exposure. This work presents the basis for a model that will inform future public health interventions and policy development, while considering the unique intricacies of traditional food systems in the context of subarctic communities in the Dehcho First Nations.

2. Study Rationale

The Dehcho First Nation is a regional council, established to represent the interests of Dene and Métis Indigenous peoples in the Dehcho region of the Northwest Territories. This regional coalition comprises a broad association of communities that are distributed throughout the southwest corner of the Northwest Territories, within the Mackenzie Valley basin. Country foods, and in particular wild-harvested freshwater fish including species such as Walleye (*Sander vitreus*), Northern pike (*Esox lucius*), Lake trout (*Salvelinus namaycaush*), and Lake Whitefish (*Coregonus clupeaformis*), are cultural linchpins and dietary staples that are an integral contributing factor to the health, wellness, and improved food security of First Nations communities in the region (Berti et al., 1998). In addition to the inherent cultural and socioeconomic benefits of these foods, wild caught fish are a primary source of omega-3 polyunsaturated fatty acids and other essential micronutrients in the diet. Fish-derived lipids are associated with a host of cardiovascular and neurocognitive health benefits (Kris-Etherton et al., 2009; Mahaffey et al., 2011). However, these benefits may be undermined by growing concerns surrounding the increasing levels of methylmercury (MeHg) in some lakes of the Dehcho. Prolonged dietary exposure to MeHg has the potential to cause permanent adverse effects to neurological, immune, cardiovascular, renal, and reproductive systems, and is particularly toxic to the developing fetus and young children (Grandjean et al., 1999).

Elevated Hg concentrations have been documented in Walleye, Northern Pike, and Lake Trout in several lakes of the Dehcho region (Evans et al., 2005), and follow up work has demonstrated a near-twofold increase in Hg levels in fish caught in some of these lakes, with decreasing or stabilizing levels in others (Swanson, 2014). Though there is an ongoing dietary transition occurring in Northern First Nations communities trending towards the consumption of

relatively greater quantities of imported market foods, there are still a number of communities that rely heavily on traditionally harvested foods in their diet. In response to evidence of elevated fish mercury profiles in some lakes of the Dehcho, the Government of the Northwest Territories (GNWT) Department of Health and Social Services developed and released a series of public health consumption notices to advise public of the potential health risks associated with the dietary consumption of several piscivorous, predatory fish (DHSS, 2016).

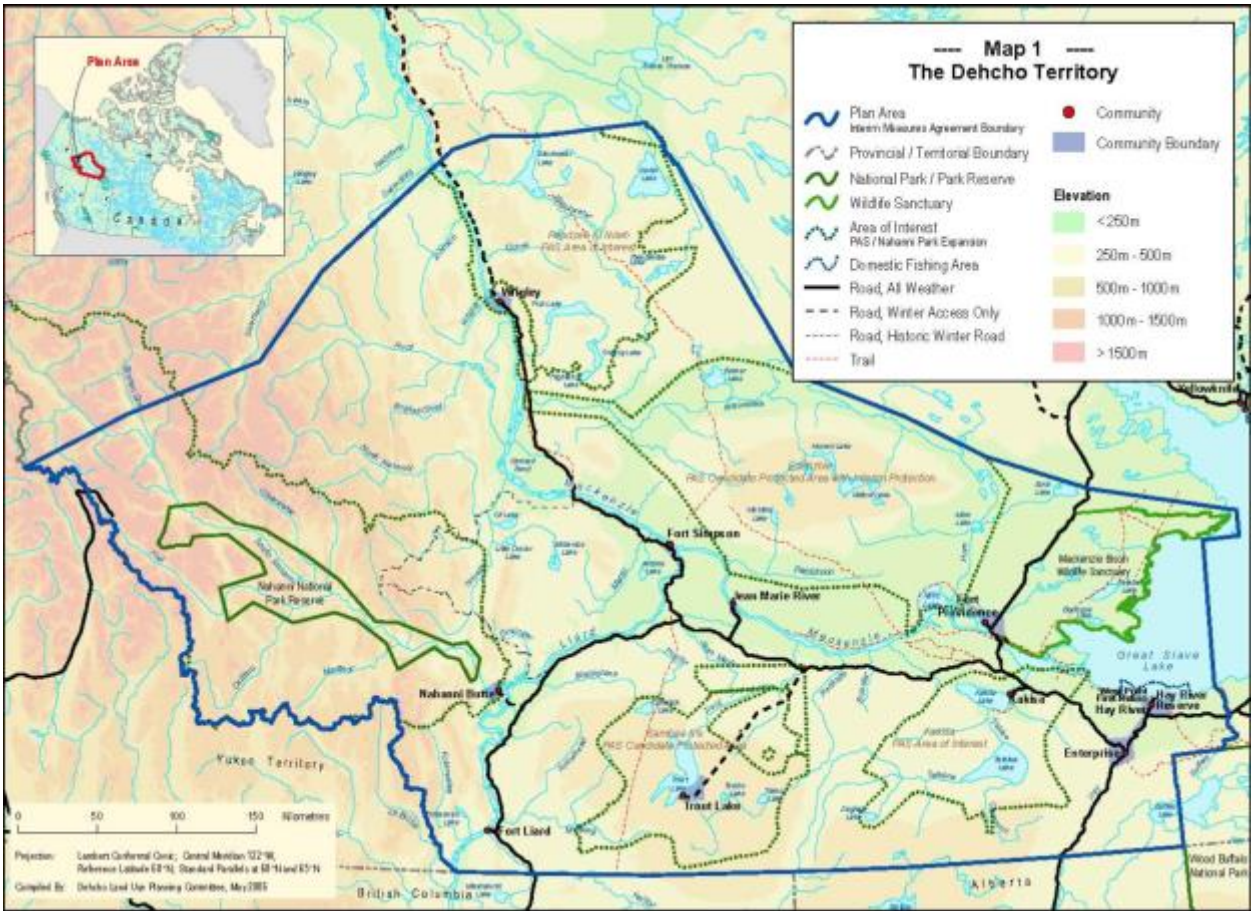


Figure 2-1. A map of the Dehcho region, with the smaller pane in the top left demonstrating the Dehcho's geographic location relative to a map of Canada (Anishnabe History, 2017).

Country food consumption notices and other relevant risk communication strategies in subarctic First Nations communities must be predicated on informed policy development that considers both the risks and benefits of country foods within a community-specific context. Contaminant advisories leading to indiscriminate reduction in country food consumption may run the risk of

instilling adverse community health outcomes in terms of nutrient adequacy and chronic disease risk (Laird et al., 2013). Effective, clearly communicated dietary interventions underscore the cultural and nutritional value of country foods in the diet, while considering the risks of exposure to environmental contaminants.

Probabilistic, population-based models can be a useful tool to estimate and characterize community-level profiles of methylmercury exposure. However, the true extent of exposure to methylmercury, and other contaminants, in First Nations peoples of the Dehcho region is not well understood. There is a degree of uncertainty surrounding food consumption patterns and toxicokinetic variability between individuals that is implicitly woven into the structure of retrospective probabilistic dose reconstruction models, which makes it difficult to draw conclusions that are specific to one person. By compiling datasets that outline regional country food consumption patterns and internal mercury and omega-3 PUFA exposure collected from a comprehensive, multi-year contaminants biomonitoring study conducted in communities of the Dehcho region, we can attempt to fit a probabilistic dose reconstruction model that characterizes population-level mercury and nutrient exposure profiles that convey important community-specific nuances. Broadly, this work will contribute to the informed development of region-specific risk-benefit communication tools and dietary interventions that promote and maximize the nutritional benefits of country foods in order to lower risk factors for chronic disease, while also making a concerted effort to minimize mercury exposure among communities in the Dehcho region.

2.1 Research Questions

In subarctic First Nations communities, maintaining country food consumption is of paramount cultural, spiritual and nutritional importance – traditional food systems play an important role in facilitating improved food security and wellbeing (Kuhnlein and Receveur, 2007). To promote the use of country foods, and to foster effective communication to First Nations communities of the intimate relationship that exists between dietary intake and exposure to environmental contaminants, the following research questions were addressed in Part I of this two-part thesis:

i. Which fish species hold the highest nutritional value, in terms of fatty acid content, relative to the amount of mercury contained within their tissues?

ii. What are the Hg and omega-3 fatty acid intake levels in five communities of the Dehcho, in comparison to the toxicological reference values and dietary reference intakes, respectively?

Part II of this thesis project evaluated and the significance of the findings from Part I, building on this work to model risk and benefit from fish consumption in participating communities of the Dehcho region. In order to accomplish this, the following research questions were composed:

iii. In communities of the Dehcho, which fish species comprise the majority of all dietary fish intake among the population?

iv. After refining the dose reconstruction model with community-specific dietary intake data and profiles for omega-3 and mercury content that were generated from Part I from locally harvested fish, can this model be corroborated by biomarker data (e.g. hair mercury, blood fatty acid profiles) from the Contaminants Biomonitoring Study?

2.2 Objectives

The following objectives were formulated in order to address the aforementioned research questions:

i. Determine the concentration of total Hg and omega-3 PUFAs in the muscle tissue of various wild-caught freshwater fish species harvested from 8 Dehcho lakes.

Using the mercury and omega-3 fish composition dataset, and the retrospective dose reconstruction model constructed in Part I of my thesis, I will address these objectives in Part II of this thesis project:

ii. Construct a probabilistic, population-based retrospective dose reconstruction model to assess dietary omega-3 fatty acid intake and Hg exposure among members of the Dehcho First Nations.

iii) Characterize and quantify sources of mercury and omega-3 PUFA exposure from locally harvested fish consumption, and identify key contributing drivers from the diet.

iv) Assess human health risk from MeHg exposure to participating communities of the Dehcho through a probabilistic model.

v) Assess the utility and accuracy of the model at estimating population-level profiles of risk and cardioprotective benefit from fish consumption using biomarkers for omega-3 PUFAs in blood plasma and Hg in hair.

3. Literature Review

3.1 Introduction

This literature review will provide an overview of existing research on the toxicology, toxicodynamics, primary sources and biomarkers of methylmercury (MeHg), and will summarize existing exposure assessment models used to characterize profiles of exposure in human populations. Additionally, this literature review will explore in detail the importance of traditional food systems and their role in contributing to a balanced diet in First Nations communities of the Dehcho region in the Northwest Territories, by examining the nutritional benefits that country foods afford to the diet. This review will briefly summarize human health effects of methylmercury; however, it should not be mistaken for a comprehensive review of existing literature pertaining to human health effects of methylmercury, as these outcomes are discussed in greater detail elsewhere (Mergler et al., 2007; Choi et al., 2008; Díez, 2009).

Country foods are invaluable to the cultural continuity, self-identification, autonomy and sovereignty of many Indigenous Canadians (Kuhnlein and Receveur, 2007). The aim of this literature review is to serve as the foundation for subsequent research that will contribute to the development of effective risk assessment profiles for methylmercury exposure in First Nations communities, and to existing food advisory guidelines for country food consumption. This information will also inform ongoing biomonitoring studies that relate mercury levels in country foods with blood and tissue levels in First Nations populations, with the end goal of maximizing nutritional intake from consumption of country foods and minimizing risk from exposure to MeHg.

3.2 Indigenous environmental health and traditional food systems

Despite the relatively high standard of living in Canadian society, Indigenous peoples of Canada experience unique disparities in health and quality of life, which are illustrated by significant inequities in health and disease outcomes between these populations and the Canadian population as a whole (see, Adelson, 2005). For example, type II diabetes mellitus afflicted over 20% of the Saskatchewan's First Nations populations in 2006, compared with only 6% among the general population in the province (Dyck et al., 2010).

Many First Nations communities in Canada are remote and rural, and as an integral part of their heritage, these populations often maintain a close and intimate connection with the environment (Beckford et al., 2010). This link often carries vital cultural, societal and spiritual implications that remain deeply rooted in the history of these people (see, Van Oostdam et al., 2005). In First Nations societies, the land is a fundamental social, cultural and spiritual component that is essential to health and wellbeing, and to the continuity of cultural values and self-identification in these communities (Richmond and Ross, 2009). This close relationship with the land can pose contaminant risks to health. Many studies have clearly identified the presence of environmental contaminants, including heavy metals (mercury and lead), organochlorines (lindane, chlordane, toxaphene, dichlorodiphenyltrichloroethane (DDT), and polychlorinated biphenyls (PCBs)) across Canadian Arctic and subarctic ecosystems (Barrie et al., 1992; Lockhart et al., 1992; Muir et al., 1999; Donaldson et al., 2010). These pollutants, which are often released to the environment in southern regions, are transported to the Arctic by long-range atmospheric transport, or by waterways and ocean currents (e.g., Donaldson et al., 2010).

Remote Indigenous communities often depend on locally harvested country foods as a part of a balanced diet (e.g., Van Oostdam et al., 2005). Traditional food systems play a vital role

in the social, cultural and economic wellbeing of many subarctic First Nations communities, with country foods providing significant nutritional and sociocultural value (Richmond and Ross, 2009). The practices of harvesting, preserving and preparing food in these communities plays a crucial role in reinforcing First Nations culture and identity (Kuhnlein and Receveur, 1996).

As these locally sourced commodities often form a substantial component of the food consumed in Indigenous communities, country foods are a key contributor of essential nutrients to the diet (Kuhnlein et al., 2004). These foods provide an excellent source of protein, long-chain omega-3 fatty acids, selenium, iron, zinc, and vitamins A, C, D, and E (Fediuk et al., 2002; Donaldson et al., 2010; Laird et al., 2013). Traditional food systems of Indigenous communities typically contain greater nutrient density overall than in imported market foods (Kuhnlein and Receveur, 1996).

Traditional food systems contribute significantly to the overall quality of the diet of First Nations peoples living in the Canadian subarctic (Kuhnlein and Receveur, 2007), and many health benefits have been suggested to result from an increased intake in country food consumption. For example, several investigators have reported on the role of a diet rich in country foods in protecting or mitigating the risk of cardiovascular disease in Indigenous populations (Blanchet et al., 2000). Additionally, many staples of a traditional diet in First Nations communities are rich in essential fats including docosahexaenoic acid (DHA, 22:6n-3) and eicosapentaenoic acid (EPA, 20:5n-3), which are thought to reduce the risk of high blood pressure, diabetes, and certain types of cancer (Beilin et al., 1993; Nielsen et al., 1996).

There has been a transitional shift in the diet of Canadian Arctic and subarctic Indigenous populations, from nutrient-dense country foods to a diet high in carbohydrates and low in essential nutrients (e.g., McGrath-Hanna et al., 2003). Obesity and other diet-driven chronic

illnesses, stemming from poor nutrition, reduced physical activity, and inflated alcohol and cigarette consumption, have emerged as health concerns in Canadian Indigenous communities (Dyck et al., 2010; Egeland et al., 2011; Lemire et al., 2015). Traditional food systems play a crucial role in preserving cultural continuity and self-identity in First Nations society, and contribute to improved food security, in communities where food insecurity is a chronic concern.

3.3 Omega-3 polyunsaturated fatty acids

3.3.1 Health benefits of omega-3 polyunsaturated fatty acids

Animal food products are considered to predominate in traditional food systems, and as a result an Indigenous diet rich in country foods is assumed to be relatively high in fat. Wild-harvested and free-range animals, which occupy an important role in traditional foods systems, are considered to have much a higher essential fatty acid content, and lower saturated fat content, than in commercial livestock (Horrocks and Yeo, 1999). The presence of high levels of omega-3 long-chain polyunsaturated fatty acids (omega-3 PUFAs), including EPA and DHA, is the basis of dietary recommendations that include the consumption of fish-derived lipids as part of a healthy diet (Mahaffey, 2004). Omega-3 PUFAs are polyunsaturated fatty acids that have a double bond at the third carbon atom from the end of carbon chain. While there are a series of long-chain polyunsaturated fatty acids, three dominate in terms of their importance to human physiology: α-linoleic acid (ALA), EPA, and DHA. Relatively shorter than its counterparts, ALA is a plant-based fatty acid found in high concentrations in flax seed, soybean, canola, and other plant-based foods (Albert et al., 2005). Though the human body can convert ALA to EPA and DHA, studies suggest that the enzymatic breakdown and synthesis of these compounds is a slow process, with a low yield (Swanson et al., 2012). Wild-harvested, freshwater fish, and other

marine seafood play an important role in traditional food systems, and are important contributors of EPA and DHA, in addition to other long-chain polyunsaturated fatty acids (Kris-Etherton et al., 2009). There are a host of health benefits conferred from a diet rich in these essential fatty acids, which are summarized below.

3.3.2 Cardiovascular outcomes

Fish or fish oil consumption in the diet mitigates cardiovascular risk factors; therefore, dietary guidelines encourage the consumption of fatty fish at least twice per week (Vázquez et al., 2014). Fish tissue contains high levels of long-chain omega-3 PUFAs, including EPA and DHA, in oily fish types (Vázquez et al., 2014). EPA and DHA carry a wide array of health benefits. For example, these long-chain polyunsaturated fatty acids play an integral role in anti-inflammatory processes in cell membranes, and are essential in fetal development (Conquer et al., 2000; Dunstan et al., 2008). Additionally, EPA and DHA are precursors of lipid mediators considered to be beneficial in preventing or treating several diseases (Swanson et al., 2012).

Strong evidence suggests the consumption of fish or fish oils lowers the risk of death from coronary heart disease, and many studies have even addressed the implications of omega-3 PUFAs in mitigating cardiovascular disease (CVD) risk factors in Indigenous cohort studies (Dewailly et al., 2001; Dewailly et al., 2002; Dewailly et al., 2003). Dewailly et al. (2001) examined an Inuit population aged 18-74 years, and considered the relationship between blood plasma concentrations of EPA and DHA and cardiovascular disease factors in this population. They observed a protective effect of n-3 fatty acids on HDL-cholesterol and triacylglycerol concentrations, which are notable risk factors associated with CVD (Jacobs et al., 1990; Gaziano et al., 1997). The findings from Dewailly et al.'s (2001) study suggested that the traditional diet may play a critical role in low mortality rate from ischemic heart disease in the Inuit population.

Similar studies have further clarified the cardiovascular benefits associated with long chain omega-3 PUFAs. Evidence from clinical trials demonstrates reduced triglyceride levels from omega-3 PUFA intake (Eslick et al., 2009), as well as lowered systolic and diastolic pressure and resting heart rate (Geleijnse et al., 2002; Mozaffarian et al., 2005), all of which are risk factors associated with CVD.

Measures to quantitatively characterize and evaluate the cardiovascular benefits associated with adequate omega-3 PUFA intake have been explored in previous studies (Harris and von Schacky, 2004). As a tool to characterize omega-3 PUFA exposure, Harris and von Schacky (2004) proposed the use of the relative percentage of EPA+DHA in total fatty acids in blood as a risk factor for coronary heart disease (CHD) mortality. This measure, which was thereafter referred to as the Omega-3 Index, was suggested as a tool to characterize levels of EPA+DHA in the blood that correspond to cardioprotective benefits associated with omega-3 PUFA intake. The Omega-3 Index categorizes four discrete groupings that correspond to EPA+DHA weight percentage values in erythrocytes of ≤4 (very low), >4-6 (low), >6-8 (moderate), and >8 (high). Equivalent groupings for other measures in blood, including plasma total lipids [≤2.9 (very low), >2.9-4.0 (low), >4.0-5.2 (moderate), and >5.2 (high)] were determined according to equations described in previous studies (Stark et al., 2016a).

3.3.3 Growth and cognitive development

Long chain omega-3 fatty acids may have a role in neurodevelopment during early stages of the lifespan (Neuringer et al., 1988). Animal studies have demonstrated marked neurodevelopmental improvements from omega-3 PUFA supplementation. In one study, young monkeys administered a diet deficient in omega-3 PUFAs including DHA and EPA demonstrated reduced visual acuity, along with many behaviours that are indicative of impeded

neurological development (Neuringer et al., 1988). In an experimental study on rats, depressive-like symptoms were reported in post-pubescent rodents whose mothers were fed a DHA-deficient diet during pregnancy, when compared with offspring who had sufficient access to DHA during development (Weiser et al., 2015). In an experimental animal study of Alzheimer's Disease, rats supplemented with omega-3 PUFAs demonstrated improved cognitive function, diminished neuronal loss, and reduced the amount of amyloid-β, a peptide that contributes to the development of plaque in the Alzheimer's brain (Hooijmans et al., 2012).

Additionally, studies have suggested a link between regular doses of DHA and other omega-3 PUFAs with improved cognitive development in infancy (Dunstan et al., 2008). Some studies, which examined maternal supplementation before birth and postpartum, found minimal differences between the control group and offspring whose mothers were given DHA supplements (Malcolm et al., 2003; Colombo et al., 2004). However, there is some evidence suggesting prenatal omega-3 PUFA supplementation (as well as supplementation during lactation) can contribute to improved neurodevelopment and cognition (Dziechciarz et al., 2010).

Furthermore, maternal EPA and DHA supplementation in pregnancy is suggested to be associated with a lowered risk of offspring developing asthma, as well as increased fetal tissue concentrations of EPA and DHA (Olsen et al., 2008; Swanson et al., 2012). In a randomized control trial (RCT) of 533 women with normal pregnancies, pregnant mothers who were administered a regular dietary supplement of EPA+DHA demonstrated lower occurrences of asthma in offspring, when compared to those who were administered an olive oil or placebo-alternative (Olsen et al., 2008). However, in other randomized control trials examining this phenomenon, few significantly consistent effects were discovered (Ruxton et al., 2004).

3.3.4 Inflammatory Disease

There is growing evidence suggesting long chain polyunsaturated fatty acids have potential immunomodulatory effects, prompting many researchers to examine the potential benefits of these fatty acids in treating chronic inflammatory disorders (Ruxton et al., 2004). Many double-blinded RCTs examining fish oil supplementation in patients with rheumatoid arthritis reported a variety of improvements in clinical outcome, including reduced morning stiffness, reduced numbers of tender or swollen joints, reduced joint pain, reduced time to fatigue, improvements in grip strength, and reduced need for non-steroidal anti-inflammatory drugs (Kremer et al., 1985; Tulleken et al., 1990; Kjeldsen-Kragh et al., 1992; Lau et al., 1993).

3.4 Human exposure to MeHg

Mercury is a pervasive global pollutant that enters the environment both naturally, through the weathering of soil and rocks, volcanic activity and from forest fires, but primarily through anthropogenic processes including industrial coal combustion, waste operations, and smelting (e.g. Health Canada, 2007; Roman et al., 2011). While elemental mercury travels and is deposited primarily through atmospheric transport, ambient air mercury levels do not constitute a significant public health risk (Clarkson et al., 2003). In contrast, as it is proven to present significant human health risks, dietary exposure to the more toxic and bioaccumulative organic form, methylmercury, is a pressing public health concern (e.g., Tian et al., 2011).

3.4.1 Sources of MeHg

Methylmercury (MeHg) biomagnifies in aquatic food chains, and bioaccumulates in the tissues of fish (e.g. Clarkson, 2002). In humans, exposure to mercury in its organic form occurs primarily as a result of consumption of higher trophic level fish (Mergler et al., 2007; Karagas et

al., 2012; Lin et al., 2014). This poses a particularly pressing concern for Indigenous environmental health; not only are fish a highly valued source of many essential nutrients, but they are also a critical component in traditional food systems across Canada (Kuhnlein and Chan, 2000).

In aquatic systems, it is understood that methylmercury is produced primarily as a result of the microbial methylation of oxidized mercury, upon which this methylmercury then enters the food chain, where it bioaccumulates in fish and marine mammals that are a part of traditional food systems (King et al., 2000; Maycock and Benford, 2007). While most human exposure to MeHg occurs predominantly as a result of fish consumption, reports of other sources (e.g. intake of foods from nearby mercury mines) exist (Malm, 1998; Horvat et al., 2003; Feng et al., 2008). For example, methylmercury was found in relatively high concentrations in rice cultivated from areas contaminated with mercury, and in the meat of terrestrial animals, and pork and chicken, likely a result of fishmeal used in livestock feed (Ysart et al., 2000; Horvat et al., 2003; Lindberg et al., 2004). However, in the subarctic Mackenzie Valley, and more specifically in communities of the Dehcho First Nation, there are no known local point sources that contribute to methylmercury exposure.

Methylmercury is the most easily absorbed and readily bioavailable form of mercury in the human gastrointestinal tract, and consequently is considered the most threatening form of Hg to the human population (Clarkson, 2002). Furthermore, past studies have demonstrated that in aquatic ecosystems, and specifically in fish tissue, the majority of mercury present exists as methylmercury (from 75-95% of HgT), and it is often assumed that total mercury (HgT) is present in its methylated form, as methylmercury (Bloom, 1992). Studies have demonstrated inconsistency in the amount of HgT present as methylmercury in fish tissue, which makes it

difficult for risk assessors to accurately model exposure in the population using a fixed conversion factor (Forsyth et al., 2004). For these reasons, human health risk assessments typically assume conservatively that 100% of ingested HgT is in the form of methylmercury, to account for the varying degree of uncertainty associated with this measure (e.g. Health Canada, 2007; Laird et al., 2009).

3.5 Toxicodynamics of methylmercury

While it is widely regarded that several servings of fish as part of a balanced diet has a range of health benefits, it is important to also consider the potential health risks posed by methylmercury exposure as a result of fish consumption. This section provides a brief summary of the toxicological effects of methylmercury in human populations.

The hazardous and diverse health effects of mercury on health have been studied extensively, and can depend on the form of mercury to which a person is exposed and the duration of exposure. Exposure to elemental mercury, which occurs primarily through inhalation, is known to cause extensive damage to the kidneys and to the central nervous system in high doses (Sherman et al., 2013). The majority of this inhaled elemental mercury is absorbed quickly into the bloodstream, and is oxidized within cells (Clarkson et al., 2007). In its liquid form, it is poorly absorbed by human tissue and represents a minimal health risk. However, as a vapour it is highly volatile and can be readily absorbed in the lungs (Clarkson et al., 2007). Exposure to inorganic mercury occurs primarily through ingestion. In large quantities, ingested inorganic mercury can lead to irritation or corrosive effects on the gastrointestinal tract (Park and Zheng, 2012). Furthermore, acute high dose exposure to inorganic mercury can result in burning chest pain and impaired kidney function, as well as contact dermatitis, discoloration of the nails, and

burning on the skin (Park and Zheng, 2012). Methylmercury is rapidly absorbed into the bloodstream from the gastrointestinal tract, and is quickly distributed throughout the body (e.g. Clarkson, 2002). A small fraction of methylmercury is broken down and converted to inorganic mercury by microflora in the GI tract, where it is poorly absorbed and thus excreted in the feces (Rowland, 1988). Methylmercury contamination in fish, particularly in deeper-dwelling, pelagic predatory fish at higher trophic levels, poses a particular challenge to public health, particularly due to the known nutritional benefits conferred through regular dietary fish consumption. The careful balance of these risks and benefits is particularly pertinent in subarctic communities of the Dehcho region, where wild-harvested freshwater fish are an important component of traditional food systems. In deeper, anoxic or oxygen-poor sediments, sulfate- or iron-reducing bacteria convert significant amounts of mercury to its organic form (Compeau and Bartha, 1985; Kerin et al., 2006). Depth-specific differences in foraging behaviour also likely play a key role in total body burden for mercury over the lifespan of a pelagic predatory fish (Choy et al., 2009).

3.5.1 Cardiovascular toxicity

Several studies report strong evidence connecting methylmercury exposure with a range of adverse cardiovascular effects. Multiple studies have demonstrated a positive association between methylmercury exposure and increased risk of atherosclerosis (Guallar et al., 2002; Choi et al., 2009). In particular, methylmercury is associated with acute myocardial infarction in several studies. Studies suggest that exposure to methylmercury increases the risk of myocardial infarction, and that elevated methylmercury levels accelerate the progression of carotid atherosclerosis (Mahaffey, 2004; Kim et al., 2014). In a population-based prospective study of 1871 Finnish males, men in the highest third of the population for hair mercury content had significantly higher risk for acute coronary events, cardiovascular disease (CVD), coronary heart

disease, as well as all-cause mortality, when compared with men in the lower two-thirds of the population (Virtanen et al., 2005). Chronic dietary methylmercury exposure among Faroese men who regularly consumed whale meat as their main source of seafood displayed cardiovascular health outcomes, including increases in blood pressure and intima-media thickness (IMT) (Choi et al., 2009). Methylmercury exposure was associated with decreased sympathetic and parasympathetic modulation of heart rate variability in Faroese children, and similar findings were demonstrated among a cohort of Nunavik Inuit children (Grandjean et al., 2004; Valera et al., 2012). This indicator is suggested to be a predictor of increased risk for cardiac events.

While there is a growing body of evidence supporting the adverse cardiovascular outcomes associated with methylmercury exposure, these results are not consistent in the literature. A prospective cohort study in the U.S. examined toenail mercury concentrations and incidence of CVD (including coronary heart disease and stroke) in a population of 51,529 men and 121,700 women. After adjustment for matching factors, study participants with higher mercury exposure did not appear to demonstrate a higher CVD risk (Mozaffarian et al., 2011). Similar findings have been reported through the use of other biomarkers. A Quebec study conducted before and after sport fishing season in James Bay demonstrated decreased levels of oxidized low-density lipoprotein (LDL), a strong predictor of cardiovascular disease risk, despite a two-fold increase in hair Hg over the same period of time (Bélanger et al., 2008).

Animal Studies

A growing body of evidence strongly supports the conclusion that methylmercury exposure contributes to oxidative stress, a preliminary biological reaction that can cause vascular cell damage and lipid peroxidation (Grotto et al., 2009; Roman et al., 2011). Oxidative stress, and subsequent formation of reactive oxygen species (ROS) and damage to the vascular

endothelium, can lead to increased risk of atherosclerosis, hypertension, and CVD outcomes (Elahi et al., 2009; Touyz and Briones, 2011).

Experimental animal studies have consistently demonstrated evidence for methylmercury-induced oxidative stress and lipid peroxidation, two contributing factors to CVD risk. Experimental studies examining long-term, chronic exposure to low levels of MeHg in rats have demonstrated an increase in systolic pressure in rats exposed to a long-term low dose of MeHg, as well as a suggested increase in ROS production (Grotto et al., 2009). In a similar study, rats administered an acute dose of mercuric chloride ($HgCl_2$) demonstrated increased hepatocellular injury from lipid peroxidation (Lin et al., 1996).

3.5.2 Neurocognitive development in early life

Although methylmercury is known to adversely affect the central nervous system at any stage in development, several notable incidents of exposure have underscored the particular vulnerability of the developing fetus to this potent organic toxicant (Harada, 1995; Debes et al., 2006; Oken and Bellinger, 2008). Despite exhibiting minimal or no symptoms of mercury poisoning, pregnant women exposed to high levels of methylmercury, gave birth to babies with severe neurological impairments, including, among others: delayed milestones of development; blindness; deafness; and, cerebral palsy (Amin-Zaki et al., 1978; Harada, 1995; Gauba et al., 2014; Rice et al., 2014). One of the more recognized examples of methylmercury exposure led to the coining of a disease now known as Congenital Minimata Disease. Extreme fetal abnormalities and neurotoxicity were reported in pregnant women exposed to highly contaminated seafood. Offspring developed symptoms ranging from microcephaly and blindness, to severe mental and physical retardation (Harada, 1995).

Results from studies of prenatal exposure to methylmercury have demonstrated adverse neurocognitive outcomes in school-aged children (Kjellström et al., 1989; Grandjean et al., 1997). In a prospective epidemiological study of births in the Faroe Islands, significant, dose-related adverse effects from prenatal methylmercury exposure were observed, using maternal cord blood and hair as biomarkers for mercury exposure from maternal consumption of pilot whale (Weihe et al., 2002). Adverse associations between methylmercury exposure and decrements in neurocognitive endpoints, including memory, attention, linguistic capacity, and visuospatial function were reported (Grandjean et al., 1997). Similarly, a New Zealand study investigating 6- and 7-year old children of mothers who demonstrated elevated hair Hg levels found a positive correlation between measures of neurodevelopment and hair mercury levels, with an association demonstrated between prenatal Hg exposure and decreased cognitive test performance (Kjellström et al., 1989). However, the Seychelles Child Development Study, a longitudinal assessment of child neurocognitive development, indicated no detectable adverse effects from prenatal MeHg exposure associated specifically with ocean fish consumption (Myers et al., 2003).

3.5.3 Neurotoxicity

The neurotoxicity of methylmercury has been extensively studied in cases of environmental exposure. Clear and tangible neurotoxic effects have been observed in devastating epidemics where environmental contamination of food sources led to exposure of the population to staggeringly high methylmercury levels (Farina et al., 2011). This toxicant can cause oxidative stress, mitochondrial dysfunction, lipid peroxidation, and interruption of synapse transmission, among other mechanisms in the brain that lead to adverse neurological outcomes (Sager and Matheson, 1988; Farina et al., 2011). In the infamous poisoning of Minimata Bay from industrial

methylmercury bioaccumulating in fish and shellfish, acute exposure to methylmercury resulted in devastating neurological disturbances, including distal sensory disturbance, impacts to visual capacity, ataxia, dysarthria, seizures, and tremor (Harada, 1995; Clarkson et al., 2003; Mergler et al., 2007). Additionally, deficits in motor, psychomotor, visual and cognitive ability have been directly connected with MeHg in several case studies of methylmercury exposure in the Amazonian Basin and in the Mediterranean (Lebel et al., 1998; Dolbec et al., 2000; Carta et al., 2003).

3.6 Selenium-mercury coexposure and toxicological implications

Despite the numerous health benefits associated with regular dietary fish consumption, fish and seafood can also present a major route of exposure to organic mercury (Mozaffarian, 2009). However, many studies have begun to examine the antagonistic relationship between selenium and mercury. Selenoproteins (including deiodinase, thioredoxin reductase, and glutathione peroxidase) have significant physiological importance, and play critical roles in thyroid function and fetal neurocognitive development (Ralston and Raymond, 2010). Selenoprotein expression is an integral component in interneuron development, and a deficiency in these proteins is associated with neurological disorders including seizures and ataxia (Ralston and Raymond, 2010).

The interaction between mercury and selenium is one of the most well-known examples of biological antagonism, however the mechanisms of their interaction require further study (e.g., Khan and Wang, 2009). Historically, dietary selenium was thought to bind Hg and prevent or mitigate its toxicity (Whanger, 1992; Yoneda and Suzuki, 1997). More recently, this interaction has been hypothesized to center predominantly around Hg's propensity to sequester selenium in

neural and endocrine systems and prevent the formation of selenium-containing proteins, and as a result the protective effects associated with selenium co-exposure may arise from adequate selenium levels so as to maintain normal selenoprotein synthesis (Ralston and Raymond, 2010). These interactions are not exclusively antagonistic, and in fact synergistic effects of Hg and Se co-exposure have been reported in the literature (Palmisano et al., 1995; Khan and Wang, 2009).

Selenium has been suggested to reduce mercury content in animal and human studies (Paulsson and Lundbergh, 1989; Seppänen et al., 2000). Seppänen et al., (2000) examined the relationship between selenium supplementation and methylmercury content in pubic hair. Compared to the control group, participants who were given a daily 100 µg selenomethionine supplement demonstrated a 34% reduction in hair mercury, with a 73% elevated serum selenium and 59% blood selenium.

The interactive effects of co-exposure to selenium and mercury have also been observed through *in vivo* studies examining these phenomena in fish tissue. A study conducted by Paulsson and Lundbergh, (1989) examined a Swedish lake with a population of fish high in mercury content. It was observed that after only one year of treatment with selenium (raising lake selenium concentrations from 0.4µg to 3-5µg/L), mercury content in fish tissue was reduced by 50-85% (depending on age and species). In a study examining *in vivo* fish exposure mercury and selenium interaction, MeHg accumulation was reduced significantly by co-exposure with Se, however it continued to present toxic inhibitory effects on antioxidative selenoproteins (Branco et al., 2012).

3.7 Human Health Risk Assessment

Understanding methylmercury toxicity and the fundamental components that influence exposure to methylmercury allows toxicologists and clinicians to assess the adverse health risks posed by MeHg exposure. The human health risk assessment process for mercury is subdivided into four critical steps: problem formulation; exposure assessment; toxicity assessment; and risk characterization (Renwick et al., 2003; Health Canada, 2007; Maycock and Benford, 2007). To identify and characterize a potential hazard, an understanding of toxicity, and the adverse health effects in the population from contaminant exposure must be understood.

3.7.1 Problem Formulation

The first phase in human health risk assessment, problem formulation consists of a screening process to identify and characterize the primary contributing aspects to human health risk: contaminants, exposure pathways, and potential receptors. In this stage, the research team develops a focused understanding of the scope of the assessment, defines the goals and desired outcome from the results of the study, and outlines all hypothesized interaction between the population, environmental contaminants, exposure, and toxicity, and how these interactions pose risks to human health (Health Canada, 2010a).

In human health risk assessment, receptors are subpopulations exposed to a contaminant of potential concern through one or more exposure pathways. The assessment of exposure is a process that should be performed for all potential human receptors for which exposure is anticipated (Health Canada, 2010a). In Indigenous communities and particular those in remote Northern Canada, country food consumption can be an important route of exposure for some contaminants. To effectively characterize risk to First Nations communities from methylmercury exposure, receptor characteristics such as age/gender distribution in the community, status in

terms of vulnerability to the toxicant, and any unique population characteristics are important details to include when assessing risk (Health Canada, 2010a). For example, as the critical health effect for methylmercury is its potent neurotoxicity, and in particular the neurocognitive implications from *in utero* and exposure early in the lifespan, pregnant women and women of childbearing age are receptors of particular interest (McDowell et al., 2004).

3.7.2 Exposure/Toxicity assessment of mercury

In the context of human health risk assessment, exposure assessment involves estimating the quantity of each chemical received by human receptors per unit time, to establish the rate or extent of exposure. Toxicity assessment involves characterizing the potential health risks associated with exposure to a particular contaminant. Unless one aspect of the toxicity assessment involves developing toxicity reference values to employ in combination with a calculated exposure or dose in the characterization of risk, this stage often involves identifying the TRVs for use in this process.

Fundamentally, exposure assessment characterizes the nature and size of a population exposed to a contaminant, and the magnitude and duration of their exposures (Paustenbach, 2000). Dietary exposure assessment is an essential tool to begin to quantify the risks associated with consuming country foods, and plays an important role in population health assessment (Kavlock et al., 1996). There is a perception of elevated health risk from eating country foods that is persistent in Canadian Indigenous communities, and a lack of communication and education between investigators and Indigenous stakeholders may further shape these beliefs (Furgal et al., 2005). Comprehensive exposure assessments are necessary to develop effective food consumption advisories without dissuading the population from consuming foods that are rich in essential nutrients and have inherent cultural and economic value (Berti et al., 1998).

Assessing human exposure to a toxicant is a process that can be evaluated in two ways: internal exposure and external exposure. To regulate external exposure, federal health agencies develop and maintain a reference dose (RfD) specific to a particular toxicant, to characterize and assess dietary exposure to environmental contaminants and to quantify the chronic effects from oral exposure. A contaminant's RfD is generally understood to be the concentration of a certain chemical that can be consumed on a daily basis throughout the lifespan, without risk of adverse health consequences, and is also known as the provisional tolerable daily intake (pTDI) (Rice et al., 2000). Toxicological Reference Values (TRVs) typically differ between regulatory agencies, and are the product of both accumulated scientific evidence and guided policy decisions. The U.S. Environmental Protection Agency (USEPA) conducts human health risk assessment for a wide range of health effects that stem from exposure harmful environmental contaminants. As part of the process of estimating human health risk in the population from contaminant exposure, exposure data must be combined with dose-response information (USEPA, 2011). Dose-response assessment is often a two-step process which involves 1) Defining the contaminant's point of departure (POD), or the point on a toxicological dose-response curve established through experimental or observational data that corresponds to an estimated low effect level or no effect level; and 2) extrapolating from the POD to a human exposure level that is not expected to result in a significant health risk. These levels are derived based on both experimental data and previous literature documenting the chronic and acute exposure of humans to mercury. For threshold chemicals, or those contaminants that are considered to exhibit adverse health effects only once a certain dose is exceeded, traditionally the No-Observed-Adverse-Effect-Level (NOAEL) and Lowest-Observed-Adverse-Effect-Level (LOAEL) approaches have been used to determine the POD in human health risk assessment, and represent the threshold dose, these

methodologies were identified to have a range of substantial limitations, including their dependence on the study sample size, dose selection, and dose intervals (Davis et al., 2011). Conceptually superior to the former methodologies, the benchmark dose method (BMD) and the lower confidence limit on the BMD (BMDL) were adopted as alternatives to address the limitations of the NOAEL approach, as a more quantitative means of deriving regulatory exposure levels including RfDs and acceptable daily intakes (ADIs) (Setzer and Kimmel, 2003). These established benchmarks represent the degree of exposure to methylmercury that corresponds to an effect on the health of the individual. In risk assessment for methylmercury, the Benchmark Dose Lower Limit (BMDL) is often used as the basis for the point of departure (Davis et al., 2011).

A person's estimated intake of methylmercury from fish products is a measure of their daily consumption of fish muscle tissue, the concentration of MeHg in that tissue, and the body weight of the individual. This calculation yields the person's daily dose of mercury, and is also known as their Estimated Daily Intake (EDI):

$$EDI\ (ug/kg\ bw/day) = \frac{\left[fish\ muscle\ intake\ \left(\frac{g}{day}\right) X\ methylmercury\ concentration\ \left(\frac{ug}{g}\right)\right]}{average\ body\ weight\ (kg)}$$

An integral part of methylmercury exposure assessment involves quantifying internal exposure and using this information in risk assessment to guide possible lifestyle or dietary changes that might need to be made. The amount of contaminant that has been absorbed and is available within the body for interaction with target organs and other significant receptors is known as the internal dose (Paustenbach, 2000). In contrast, the delivered dose is the amount of contaminant that, after the internal dose has been metabolized, is transported to a specific tissue, organ or fluid of interest (Clewell III, 1995).

Health risk assessments and biomonitoring guidance values allow researchers, clinicians and public health officials to evaluate individual- and population-level risk to methylmercury exposure, and to regulate changes in policy that reflect this risk (Legrand et al., 2010). In Canada, initial biomonitoring guidance values that reported on the risks of methylmercury were adopted based on recommendations from a study that determined that the lowest blood concentration of the toxicant associated with adverse health effects in adults was approximately 200 µg/L (Berglund, 1971). The derivation of this value was based on findings reported in studies examining widespread outbreaks of methylmercury poisoning in Japan and Iraq.

The results of this study became the scientific basis by which the World Health Organization (WHO) established biomonitoring guidance values for methylmercury, including a Tolerable Weekly Intake (TWI) for methylmercury of 3.3 µg/kg/week, which Health Canada expressed as a provisional Tolerable Daily Intake (pTDI) of 0.47 µg/kg/day, and 0.2 µg/kg/day for women of child-bearing age and children under the age of 12 (Legrand et al., 2010). The pTDI for vulnerable risk receptors including pregnant women, women of childbearing age, infants, and young children, was adopted in response to two large prospective epidemiological studies in the Faroes and Seychelles Islands, which investigated the neurocognitive effects in children exposed to chronic low level prenatal methylmercury exposure (Budtz-Jørgensen et al., 2000; Van Wijngaarden et al., 2006; Legrand et al., 2010). Table 3-1 summarizes Health Canada's derived blood methylmercury guidance values and recommendations for monitoring and intervention based on blood level and age-sex category (Legrand et al., 2010). These guidelines take into account age, sex, and subjects with increased vulnerability or sensitivity, such as pregnant women.

Table 3-1. Overview of Health Canada's blood and hair MeHg guidance values (adapted from Legrand et al., 2010).

Age-Sex Category	Blood Guidance Levels (µg/L)	Hair Guidance Levels (mg/kg)	Recommended Follow-up
Pregnant Women **Females birth-49 years** **Males ≤ 18 years**	<8	<2.4	No follow-up required
Pregnant Women **Females birth-49 years** **Males ≤ 18 years**	8 – 40	2.4 – 12	Hair/blood test repeated after 6 months Provide dietary advice
Pregnant Women **Females birth-49 years** **Males ≤ 18 years**	>40	>12	Repeat hair/blood test immediately Review exposure history and provide dietary advice
Females ≥ 50 years **Males > 18 years**	<20	<6	Level considered "acceptable" No follow-up required
Females ≥ 50 years **Males > 18 years**	20 – 100	6 – 30	Level considered "at increasing risk" Repeat hair/blood test after 6 months Provide dietary advice
Females any age **Males any age**	>100	>30	Level considered "at risk" Repeat hair/blood test immediately Review exposure history and provide dietary advice Refer participant to physician or medical toxicologist to check basic neurological signs/symptoms

3.7.3 Human Biomonitoring in exposure assessment

Human biomonitoring is a valuable study tool that is widely used in human health risk assessment to monitor and quantify exposure to chemical contaminants (Knobeloch et al., 2011). Human biomonitoring studies are the basis behind deriving and evaluating risk management strategies for environmental contaminant exposure (Dong et al., 2015). Biomonitoring is a key tool used to quantitatively measure contaminant exposure, and can be used in a number of applications: to identify priority pollutants for which further risk management is warranted; to determine baseline exposure among a population; to compare levels of exposure between subpopulations; and to assess the effectiveness of existing human health risk management strategy. Biomonitoring studies provide an efficient and cost-effective means of identifying chemical exposure and any trends or changes in exposure. Exposure estimates from human biomonitoring allow researchers and clinicians to evaluate individual, occupational and

population health risks, and guide public health recommendations that are specific to an individual's age, gender, and level of exposure (Legrand et al., 2010).

Biomarkers are broadly defined as measurable changes in physiological systems that are caused by exposure to an exogenous substance (Metcalf and Orloff, 2004). The matrices used in biomonitoring studies contain indicators of current or previous contact with an environmental contaminant or its metabolites, and can help to quantify past and present exposure in order to effectively characterize risk at an individual and population level. Biomarkers of contaminant exposure are selected based on their sensitivity, specificity, biological relevance, practicality, availability and cost-effectiveness (Metcalf and Orloff, 2004). Community biomonitoring studies often incorporate biomarkers that meet as many of these criteria as possible, and vary depending on the chemical or metabolite being tested.

Several biological matrices are frequently employed in human biomonitoring studies. Human hair is a stable, non-invasive matrix that is often selected for use in biomonitoring for its ease of collection, low cost, ease of transport and storage, and information about both short- and long-term exposure (Angerer et al., 2007; Zhang et al., 2007; Esteban and Castaño, 2009).

Blood is a matrix often used in biomonitoring studies, and is ideal in that it comes into contact with the entire organism, and is in equilibrium with the tissues and organs where chemicals are deposited. However, drawing blood is an invasive practice, and this is understood to be the primary disadvantage of using blood as a matrix in biomonitoring assessments (Bergdahl and Skerfving, 2008). Blood is often considered a more effective indicator for the absorbed dose of mercury and therefore of MeHg exposure (Budtz-Jørgensen et al., 2005). In studies of prenatal methylmercury exposure and the imprecision of exposure biomarkers, Budtz-Jørgensen et al., (2005) determined that umbilical cord blood is the best indicator of prenatal

MeHg exposure. Blood gives an estimate of exposure over the most recent 1-2 half-lives (with a half-life of 50-70 days on average for MeHg).

Studies have demonstrated possible differences in the toxicokinetics of methylmercury between males and females in the blood (Grandjean et al., 1997). Experimental animal studies have demonstrated higher overall methylmercury retention in female rats; however, male rats demonstrated greater retention in the kidneys than females (Nielsen et al., 1996; Hultman and Nielsen, 2001). Epidemiologic studies suggest there may be a difference in the extent of developmental deficit influenced by methylmercury between males and females. In a prospective cohort study conducted by Grandjean et al., (1997), young males exposed to relatively higher prenatal mercury were demonstrated to exhibit poorer cognitive results than the controls, as measured through a series of tests. In contrast, no significant difference was reported between the two groups of girls on the same tests.

Human hair is a stable bioindicator of methylmercury exposure with many advantages for human biomonitoring (Esteban and Castaño, 2009). As methylmercury is the dominating species of mercury in hair, total hair mercury is often used to quantify methylmercury exposure in humans (Berglund et al., 2005). Hair is often used in other metals analyses, including measurements of cadmium and lead (Esteban and Castaño, 2009). Hair is considered to be an effective indicator for occupational and environmental lead exposure (Esteban and Castaño, 2009). Scalp hair is often touted as the preferred matrix for biomonitoring of chronic methylmercury exposure (Clarkson et al., 2003; Legrand et al., 2010). Scalp hair methylmercury reflects long-term exposure, and as it is relatively non-invasive to collect scalp hair, this matrix serves as an effective alternative to blood mercury analysis. Mercury from the blood enters the hair follicles, and exposure over time can be represented in hair strands (Dolbec et al., 2001). In

this role, hair serves as an effective indicator of previous blood mercury concentrations, and has also been used to estimate fetal and postnatal exposure during pregnancy and lactation (Cernichiari et al., 1995; Barbosa et al., 1998; Morrissette et al., 2004). When current exposure estimates are needed however, hair nearest to the scalp is best indicator of recent MeHg concentrations in the body (Díez, 2009). Approximately 80-95% of total mercury in hair exists as organic MeHg (Mergler et al., 2007). There are, however, some notable disadvantages or limitations to sampling hair in human biomonitoring for MeHg. For one, maternal-hair Hg is kinetically more distant from fetal circulation than cord blood Hg, and for an assessment of fetal exposure during gestation, this metric may not be as accurate (NRC, 2000). Furthermore, segmental hair analysis is subject to variability in hair growth rates, which make it difficult to identify corresponding periods of exposure (NRC, 2000).

Several studies have also suggested the use of toenails as an indicator of mercury exposure (Rees et al., 2007). Toenail mercury concentrations are known to be stable indicators of exposure over time, and it has been confirmed that toenail mercury content and fish consumption are significantly correlated (Macintosh et al., 1997; Rees et al., 2007). Employing toenails in an assessment of mercury exposure has a host of other benefits as well: toenails are relatively convenient to collect; the medium has relatively low susceptibility to external contamination; and the sample can be used as a long-term biomarker of exposure (Garland et al., 1993). Other non-invasive matrices commonly used in biomonitoring studies include, breast milk, saliva, meconium, and urine. Urine is typically the preferred non-invasive matrix in heavy metals biomonitoring studies, however, it is not typically used as a biological indicator to quantify body burden of MeHg. While urine is an effective and practical means of monitoring exposure to

inorganic mercury, urinary mercury levels may not accurately reflect body burden levels from dietary methylmercury exposure (Morton et al., 2004).

Biomonitoring has been implemented to study population-level exposure to methylmercury in human health risk assessment. Guidance values produced by these studies help to inform consumption advisories for dietary fish intake in Indigenous communities, especially for pregnant women, women of childbearing age and other vulnerable risk receptors including infants and young children. Mercury concentrations in blood or scalp hair have been widely implemented as biomarkers for methylmercury exposure (Grandjean et al., 1999; Angerer et al., 2007), and each matrix provides distinct advantages in the human biomonitoring of mercury exposure (Mergler et al., 2007).

3.7.4 Risk characterization and communication

Risk characterization is a detailed process that requires input from a range of disciplines, and involves dedicated stakeholders and community participants in the decision-making process (Paustenbach, 2000). Risk characterization is the product of all components involved in risk assessment: identifying and characterizing the hazard posed to a population, and determining the nature and toxicity from exposure to a particular contaminant (magnitude, duration, frequency, dose) in the population of interest (Renwick et al., 2003). Risk characterization involves conveying the nature of a particular risk that is associated with a given hazard, as well as the degree of uncertainty associated with that risk. This information is used to inform policy decisions and to effectively articulate the risk of exposure to the community (USEPA, 2015). The output of a risk assessment – essentially the characterization of risks posed to the population – must be conveyed in a way that is usable in risk management, and in a way that facilitates recognition and understanding for all stakeholders involved in the study (Renwick et al., 2003).

Fundamentally, to quantify and characterize risk, the estimated exposure to a contaminant in the population is compared to the corresponding TRV. The subsequent evaluation includes an assessment of whether the predicted risks or hazards are acceptable, tolerable, or essentially negligible, as well as a quantitative or qualitative assessment of any uncertainty associated with the prediction of risk.

Health Canada considers estimated daily intake values for all threshold contaminants against their respective provisional Tolerable Daily Intake values to characterize risk from dietary exposure. Hazard quotients, calculated as the ratio of the EDI (exposure) to the pTDI (reference dose), and expressed as a percentage (EDI/pTDI x 100%), are often used to identify exposure scenarios where the TRV may be exceeded in certain receptors (Health Canada, 2007).

3.8 Risk-benefit assessment and communication

Contamination of traditional food systems from industrial processes has exacerbated the risk of exposure to various organochlorines, heavy metals and radionuclides in Aboriginal communities (Furgal et al., 2005). It is essential to consider the critical role that country foods have in contributing to a balanced diet, as well as the inherent cultural and spiritual value they hold, in order to manage and communicate this risk within First Nations communities (Van Oostdam et al., 2005). Effective risk communication plays an integral role in community awareness (Donaldson et al., 2010; Driedger et al., 2013). Conveying the contaminant risks, as well as the nutritional benefits, in a clear, meaningful and accessible manner is a challenging but essential part of addressing contaminants in traditional food systems (Donaldson et al., 2010).

A study conducted by Ginsberg and Toal, (2009) incorporated a multivariate approach to the risk-benefit analysis of methylmercury exposure from fish consumption. On a species-

specific basis, they constructed dose-response relationships for omega-3 FA and MeHg for common endpoints, including cardiovascular disease in adults (represented by CHD mortality or first myocardial infarction) and neurodevelopment in 6-month old infants (represented by visual recognition memory, or VRM). Their integrated risk-benefit analysis demonstrated risks and benefits of seafood consumption by species, by measuring either the predicted change in VRM score, or by estimating the percent improvement in relative risk (Ginsberg and Toal, 2009). Their study underscored the importance of including species-specific fatty acid data in risk analysis. Predatory fish species are often higher in mercury and relatively lower in omega-3 fatty acids than other wild-harvested freshwater fish species (Reyes et al., 2017). Risk management intervention and food advisories should incorporate healthy dietary strategies that maximize the nutritional benefits of these country foods, while minimizing methylmercury exposure.

Regional representatives, local and territorial governments, and Indigenous groups act to ensure that any health-related questions are addressed, and that the risk assessment and management process takes into consideration community-specific objectives (Van Oostdam et al., 2005). Community leaders bring local knowledge and cultural perspectives that are region-specific, an integral component of risk management and communication to the local population. Community stakeholders and risk management coordinators must always be aware of the potential for food consumption advisories and other tools for risk communication to affect country food use in communities where these products comprise an essential part of a balanced diet (McAuley and Knopper, 2011). Poor risk communication practices can increase fear and confusion in Indigenous communities, and prompt significant modifications to dietary behaviour and traditional lifestyle (Furgal et al., 2005; McAuley and Knopper, 2011). As the consumption of fish confers nutritional and cultural benefits in First Nations communities, but also underlying

risks, advisories issued by government agencies may introduce the possibility of a trade off in risk (Graham and Wiener, 1997). Consumers who heed the warnings of these advisories may successfully reduce their risk of methylmercury exposure – however, they may also incur other potentially adverse health outcomes associated with reduced intake of the important nutrients (e.g., omega-3 PUFAs, selenium, vitamins, and other essential micronutrients) that fish provide in the diet (Cohen et al., 2005). Broader impacts include shifts in cultural practices, as well as impacts to the economy and health of these communities as a whole (Furgal et al., 2005).

While the net health benefits of traditional food systems, specifically fish, have been studied extensively, the risk-benefit process of quantifying the adverse outcomes associated with methylmercury exposure and the benefits of fish consumption will need to adopt a more comprehensive and multidisciplinary approach to better inform local food consumption advisories in the future (McAuley and Knopper, 2011). It is essential to consider the critical role that country foods have in contributing to a balanced diet, as well as the inherent cultural and spiritual value they hold, in order to effectively communicate risk within First Nations communities (Seabert et al., 2014). Maintaining adequate nutritional intakes from country food sources while minimizing the risks of methylmercury exposure remains a necessary goal for public health legislators (Canada's Public Policy Forum, 2015). The work described herein incorporates results from the contaminant biomonitoring study conducted in communities of the subarctic Dehcho region, and functions to characterize community-level methylmercury and fatty acid exposure in these First Nations bands. Using biomarkers of mercury exposure and a growing dataset containing mercury and fatty acid profiles in wild-harvested freshwater fish caught in lakes of the Dehcho region this study constructed a probabilistic dose reconstruction

model that will function as a component of future efforts to estimate and characterize the risks and benefits of country food use in First Nations communities of the Canadian subarctic.

4. Contaminant Risks versus Nutrient Value in Wild-Harvested Fish of the Dehcho Region, Northwest Territories, Canada

4.1 Introduction

Fish constitutes a significant dietary source of protein, omega-3 polyunsaturated fatty acids, and other essential micronutrients, and is an important resource and staple that contributes significantly to subarctic dietary quality (Kuhnlein and Receveur, 2007; Domingo, 2016). Wild-harvested freshwater fish play a particularly important role in the traditional food systems of First Nations communities of the Northwest Territories, Canada (Kuhnlein and Receveur, 1996). Traditional food systems contribute to cultural continuity, autonomy, and sovereignty of these First Nations communities, and are an important component of Indigenous sociocultural practices and identity (Kuhnlein et al., 2006; Fieldhouse and Thompson, 2012). These food systems reinforce the strong ties to the land that subarctic First Nations communities possess, and provide important alternatives to the more limited and costly range of imported foods typically available in remote Northern populations (Van Oostdam et al., 2005; Gagné et al., 2012).

The consumption of country foods, which are derived from the local natural environment, can be a major route of exposure for environmental contaminants, particularly mercury, in the Canadian subarctic (e.g., Donaldson et al., 2010). The presence of environmental contaminants, such as mercury, in the Canadian subarctic environment has continued to receive attention over the past several decades, and represents an increasingly complex public health concern (Mergler et al., 2007). Important information on the safety and sustainability of traditional food systems has been generated. The Arctic and subarctic are geographic sinks for mercury; anthropogenic

Hg emissions, climate change, and long-range atmospheric and oceanic transportation all contribute to greater availability of this global pollutant for microbial methylation of Hg (II) and subsequent biomagnification in aquatic trophic systems as methylmercury (Tian et al., 2011). Methylmercury, which is particularly well absorbed from the human gastrointestinal tract into the bloodstream, is considered the most threatening form of Hg to public health. Dietary exposure to elevated levels of methylmercury is associated with an increased risk to a range of adverse neurological, cardiovascular and immune health effects in human populations (Byczkowski et al., 2005). Furthermore, methylmercury exposure *in utero* and in early childhood poses significant risks to the neurocognitive development of children. Consequently, children, pregnant women, and women of childbearing age are potentially sensitive subpopulations for adverse health outcomes associated with elevated methylmercury intake (Mahaffey et al., 2011).

Locally harvested freshwater fish provide nutritional, cultural and socioeconomic benefits to subarctic First Nations communities. Fish are excellent sources of long-chain omega-3 PUFAs, including eicosapentaenoic acid and docosahexaenoic acid, the benefits of which inform recommendations to include fish and seafood as part of a balanced diet (Mahaffey et al., 2004; Health Canada, 2011). Strong evidence suggests the consumption of fish or fish oils lowers the risk of death from coronary heart disease, and several studies have addressed the implications of omega-3 PUFAs in mitigating cardiovascular disease risk factors in other Indigenous populations (Dewailly et al., 2003). Studies have further clarified the positive cardiovascular benefits associated with long chain omega-3 PUFAs. Evidence from clinical trials demonstrated a reduction in triglyceride levels from omega-3 PUFA consumption (Eslick et al., 2009), as well as lowered systolic and diastolic pressure and lowering of resting heart rate (Geleijnse et al., 2002; Mozaffarian et al., 2005).

Furthermore, EPA and DHA are critical to healthy neurocognitive and ocular development *in utero* and in childhood (Harris et al., 2009; Bloch and Qawasmi, 2011). For example, there are associations between maternal fish and fish oil consumption and increased visual acuity in newborns; improved scoring under a battery of assessments designed to test neurocognitive development; and a reduced propensity to developing a range of neurological disorders including attention deficit disorder, Alzheimer's disease, and schizophrenia in later stages of the lifespan (Uauy et al., 2003; Calon and Cole, 2007; Dunstan et al., 2008; Bloch and Qawasmi, 2011). Omega-3 PUFAs have also demonstrated protective effects against various inflammatory conditions, including bowel diseases, asthma, and arthritis (Dewailly et al., 2003; Bisgaard et al., 2016). Given the magnitude and variety of these benefits of fish consumption, it is important to consider the balance between the benefits of fish-derived nutrients when characterizing the risks posed by contaminants in these same food fish species.

The primary objective of the present study was to characterize mercury and fatty acid profiles in fish species harvested in freshwater lakes of the Dehcho region, Northwest Territories, Canada. In addition, this research explored the utility of nutrient:contaminant ratios as a means for identifying which foods best meet recommended fatty acid intakes while limiting Hg exposure. We hypothesized that mercury and fatty acid profiles and ratios would differ by species and lake. In addition, we hypothesized that mercury and fatty acid composition would be significantly correlated within some species.

4.2 Methods

4.2.1 Fish Sample Collection

In 2013-2015, eight wild-caught freshwater fish species, including Burbot (*Lota lota*; also known as Loche or Mariah), Cisco (*Coregonus artedi*; also known as Herring), Lake Trout

(*Salvelinus namaycush*), Lake Whitefish (*Coregonus clupeaformis*), Longnose Sucker (*Catostomus catostomus*), Northern Pike (*Esox lucius*; known locally as Jackfish), Walleye (*Sander vitreus*; also known as Pickerel) and White Sucker (*Catastomus commersoni)* were harvested from eight lakes in the Dehcho region of the Northwest Territories (including Ekali, Trout, Sanguez, Tathlina, McGill, Gargan, Mustard, and Kakisa Lakes). Fork length, wet weight, sex, and maturity were determined onsite. The sampling periods (the month of August in each of 2013, 2014, and 2015) reflected optimal seasonal conditions and represented the time of year where locally-caught fish are most frequently harvested and consumed among Dehcho communities. Of these samples, 333 (135 samples from 2013, 98 samples from 2014, and 100 samples from 2015) were selected for the measurement of both mercury and fatty acid levels. As is common practice of Indigenous fishers of the Northwest Territories, results from Longnose and White Suckers have been pooled together for the purpose of this research to reflect the lack of distinction made in subarctic First Nations communities. Sampling, handling and processing of fish followed experimental protocols approved by the University of Waterloo Animal Care Committee. All procedures on animal tissues (samples were harvested and provided by subsistence fishers) were performed in accordance with protocols approved in permit A-13-03. The necessary research permit was provided by the Aurora Research Institute (License 16046).

4.2.2 Mercury Analysis

Sample Preparation

10-50mg of fish muscle tissue was weighed, with this variation in weight based primarily on fish sample size and concentration of mercury in the sample, based on species. For example, 10 mg of tissue was prepared and weighed for smaller samples, and 50 mg sampled for those

samples that corresponded to species with relatively lower levels of Hg. Subsequently, muscle tissue was separated, and samples were freeze dried and pulverized without fish skin prior to analysis.

Mercury Analysis

Freeze-fried, homogenized fish muscle tissue samples were analyzed for total Hg on a Milestone® DMA-80 Direct Mercury Analyzer using methods described in the U.S. Environmental Protection Agency method 7473 (USEPA, 2000). Fish tissue samples were weighed into sample boats on an analytical balance. The boats were then inserted into the DMA-80, where the sample was dried and then thermally decomposed in a continuous flow of oxygen (O_2). The combustion products are carried off in the gas, and then further decomposed in a hot catalyst bed. The Hg vapours are trapped in a gold amalgamator tube and desorbed for spectrophotometric quantitation at 254 nm. The calibration detection limit was 1 ng/g. Blanks (an empty quartz boat), duplicates, and certified reference materials (CRM) were analyzed in every batch of 40 samples. At least 5 blanks were analyzed per batch. The mean blank value ± standard deviation (S.D.) was 0.02 ± 0.06 ng Hg (n=66) and this corresponded to approximately 0.05% of average fish Hg concentrations. In each batch, a CRM (either DORM-2 or TORT-3) was analyzed at the start of each run and after every 10 samples. The % recovery ± S.D. of HgT for DORM-2 and TORT-3 was 4.47 ± 0.032 mg/kg Hg (102.38 ± 5.40%) and 0.292 ± 0.022 mg/kg Hg (96.27 ± 4.83%), respectively. All values were within the certified range. Duplicates were run every 10 samples and % difference among duplicates was 4.3%. Logistical constraints imposed by field sampling conditions precluded the precise measurement of sample weight in the field. As per previously described methods, to report wet weight Hg concentration in this study, the moisture content of fish samples were assumed to be 80% (Swanson and Kidd, 2010).

Calculation of Mercury Content in Fish

Results for the total Hg were calculated as follows:

$$[Hg]\frac{ug}{g} = \frac{\left[\left(PS - \frac{PB}{A}\right)\right]}{\frac{1000}{w}}$$

Where:

PS = Average peak height or peak area of sample

PB = Average of peak height or peak area of blank

A = Slope of the calibration curve in ng/units

w = weight of freeze dried tissue in grams

4.2.3 Analysis of Fatty Acids in Fish Tissue

Approximately 10 g of frozen muscle tissue from each fish sample was pulverized in a Cryo-Cup Grinder (BioSpec Products, Bartlesville, OK, USA), chilled with liquid nitrogen (N_2), and stored at -80°C until lipid analysis was conducted, to prevent heat generation (Kitson et al., 2009). Between 10 and 30 mg of pulverized fish muscle tissue from each sample was homogenized with 3 mL of 2:1 chloroform:methanol solution. For fatty acid composition of total lipids, ethyl docosatrienoate (22:3*n*-3 ethyl ester, Nu-Chek Prep Inc., Elysian, MN) was included as the internal standard (Folch et al., 1957; Marks et al., 2013). 50 µg/mL of butylated hydroxytoluene was incorporated in the extraction reagents to prevent oxidation (Marks et al., 2013). 500 µg of 0.2 mol NaHPO4 buffer was added, and the sample was inverted 2-3 times prior to centrifugation. Each sample was then centrifuged at 1734 *rcf* for 5 minutes, and the organic phase was collected. The organic phase was evaporated under N_2 gas and 300 µL of hexane and 1000 µL 14% BF_3 in methanol was added to the dried extract. Samples were then

placed on a heating block at 95°C for 1 hour. Samples were cooled to room temperature, and 1000 µL each of both ddH2O and hexane were added. Samples were vortexed and centrifuged at 1734 *rcf* for 5 minutes. The hexane layer containing fatty acid methyl esters was collected and was evaporated again under a stream of nitrogen gas. Samples were reconstituted into 65 µL of hexane and stored in GC vials until analysis.

Total lipid extracts were separated by fast-gas chromatography (Stark and Salem, 2005). A Varian 3900 gas chromatograph equipped with a DB-FFAP 15 m x 0.1 i.d. x 0.1 µm film thickness, nitroteraphthalic acid-modified polyethylene glycol capillary column was used (J and W Scientific from Agilent Technologies, Mississauga, ON) using hydrogen (H_2) as the carrier gas. The flame ionization detector was set at 300°C with air and N_2 make-up gas flow rates of 300mL/min and 45 mL/min, respectively, with an autoinjector heated to 250°C, with a sampling frequency of 50Hz. A split ratio of 200:1 was used. A series of temperature programme rates were implemented to resolve all peaks in the fatty acid methyl esters standard. The initial temperature was 150°C with a 0.25-minutehold, followed by a 35°C/min ramp to 200°C. An 8°C/min ramp followed until 245°C was reached, where the temperature was held for 15 minutes. Peaks were identified by retention time by comparison to retention times of an external standard mix (GLC-462, Nu-Check Prep, Elysian, MN, USA). The LOD was 0.151 ng of fatty acid per 1 µl solvent (hexane) for all fatty acids. Additionally, the repeatability of the results was assessed by analyzing two samples in triplicate and 11 samples in duplicate to determine the coefficients of variation within samples. Among duplicates and triplicates, the coefficients of variation ranged between 0.2% and 7.6%.

4.2.4 Derivation of *De Minimus* Ratios

A study published by Tsuchiya et al. (2008) described the use of *de minimus* ratios as a preliminary quantitative approach for the risk-benefit analysis of fish consumption. This approach employed a dietary recommended intake (DRI) for DHA of 100 mg/day and the US reference dose (RfD) for mercury of 0.1 µg/kg/day. The nationally-established US reference dose of 0.1 µg/kg/day represents a threshold of toxicity for mercury, and is a useful measure to gauge the potential health effects of this contaminant at other doses. Tsuchiya et al. (2008) used these reference values, along with an assumed body weight of 60 kg and a daily fish consumption rate of 60 g/day, to establish and define an intake ratio of 17 mg DHA to 1 µg Hg for fish that was *de minimus*:

$$DHA_{mr} \times \left(\frac{1}{CR}\right) : TRV \times \left(\frac{1}{CR}\right) \times BW$$

where DHA_{mr} is the minimum daily recommended intake of DHA (in mg/day); CR is the daily consumption rate (in g/day); TRV is the toxicological reference value for mercury for pregnant women and women of childbearing age; and BW represents body weight (in kg). The *de minimus ratio* represents the minimum ratio of DHA intake to mercury exposure that a person should have from consuming fish, in order to meet the daily recommended intake for DHA while not exceeding the TRV for mercury (Tsuchiya et al., 2008). In a previous study, this approach was updated to better reflect the regulatory context adopted and promoted in Canada (Reyes et al., 2016). Herein, the approach was further refined to include more current recommendations for DHA intake (200 mg/day) (ISSFAL, 2004; Koletzko et al., 2008; FAO, 2010). Additionally, the bodyweight assumption was revised according to that used for the derivation of Health Canada's TRV for mercury (i.e., 65kg). Furthermore, to examine the role of lipid group in risk-benefit analysis under *de minimus* ratios, *de minimus* reference values for other lipid groups (e.g.

EPA+DHA, and total omega-3 FAs) are reported herein (ISSFAL, 2004; Koletzko et al., 2008; FAO, 2010). Reference intakes for these other lipid groups, including 250 mg/day for EPA+DHA (EFSA, 2010; Williams et al., 2017) and 500 mg/day for total omega-3 PUFAs (Kris-Etherton et al., 2007), have been cited as adequate intakes for both the general population as well as women of childbearing age.

4.2.5 Statistical Analysis

All statistical analyses were conducted using JMP Pro® version 12.2.0 (Sas Institute Inc., Cary, NC, USA) and Sigma Plot® version 12.5 (Systat Software Inc., San Jose, CA, USA). When appropriate, $\log_{10}$ transformations were used to generate normally distributed data for statistical analyses. Species- and lake- specific values for HgT and measures of lipid composition, including EPA+DHA, EPA+DHA+DPA (EPA+DHA and omega-3 docosapentaenoic acid), total omega-3 PUFAs, and total PUFAs, were calculated for fish harvested from the Dehcho region, NT. The nonparametric Spearman's rank order coefficient was chosen to measure the strength of association between variables due to the smaller sample sizes within some species, and the lognormally-distributed species-specific total mercury and omega-3 PUFA levels in fish tissue. Pearson Product-Moment correlation analyses were conducted to examine the relationship between fork length with fish tissue levels of total mercury, after log-transforming these variables to meet assumptions of normality. For the purposes of this research, a subset of fish was analyzed for both fatty acids and Hg, from a larger dataset. Paired information for Hg and fatty acids was facilitated through this subset, while the larger dataset contains more data for Hg and fork length profiles.

To determine the presence of any species-specific differences in Hg and omega-3 PUFA between lakes, fish Hg concentrations were compared among lakes using a series of one-way

analyses of covariance (ANCOVA) models. As fish Hg is often related to body size, Hg concentrations were compared among lakes and species with fork length (FL) included as a covariate. Differences between lakes for Burbot, Cisco, and Sucker were omitted from this analysis as sample sizes for these species precluded any significant findings. Whenever size-adjusted least-squared means (LSMEANS) were calculated in the ANCOVA analyses, a standardized fork length of either 450 mm or 650 mm was used as the covariate level of comparison. These fork lengths were within the range of sizes captured in each species; no extrapolation was necessary.

4.3 Results

Fish composition analyses (e.g., levels for total mercury (HgT), EPA+DHA, EPA+DHA+DPA, total omega-3 PUFAs, and total PUFAs) were completed for the muscle tissue of Burbot, Cisco, Lake Trout, Lake Whitefish, Northern Pike, Sucker, and Walleye.

4.3.1 Species- and Lake-Based Differences in Mercury and Lipids

After pooling results across all years and lakes sampled, arithmetic mean HgT concentrations within piscivorous fishes (e.g. Northern Pike, Walleye, Burbot and Lake Trout) were up to 7.3 times higher than observed in benthivorous and planktivorous fishes (e.g. Cisco, Lake Whitefish, and Sucker) (**Table 4-1**). The unadjusted arithmetic mean for tissue HgT in all species fell below the commercial sale standard of 0.5 µg/g wet weight applied by the Canadian Food Inspection Agency. However, mercury concentrations in Northern Pike, which was the most frequently caught species over the course of the three-year study, were up to six times the commercial sale guideline. Consistent with results from previous studies reporting on mercury concentrations in fish harvested from Dehcho lakes, Northern Pike demonstrated the highest

mean tissue mercury concentrations among species harvested in lakes of the Dehcho (Evans et al., 2005; Lockhart et al., 2005).

Predictably, tissue levels of mercury increased with fish size. After log-transformation, strong positive linear relationships (r=0.95, n=14, P<.0001 for Burbot; r=0.81, n=21, P<.0001 for Cisco; r=0.70, n=51, P<.0001 for Lake Trout; r=0.72, n=68, P<.0001 for Lake Whitefish; r=0.73, n=85, P<.0001 for Northern Pike; r=0.57, n=35, P=0.0003 for Sucker; r=0.78, n=59, P<.0001 for Walleye) were demonstrated for HgT and fork length for all species.

Table 4-1. Total mercury concentration in wild-harvested freshwater fish caught in the Dehcho region, Northwest Territories, Canada (2013, 2014, 2015).

Fish Species	N=333	Mercury (µg/g)	
		Range	Mean ± SD
Burbot	14	0.090 - 0.551	0.244 ± 0.130
Cisco	21	0.034 - 0.194	0.064 ± 0.045
Lake Trout	51	0.079 - 0.643	0.223 ± 0.121
Lake Whitefish	68	0.021 - 0.320	0.094 ± 0.061
Northern Pike	85	0.036 - 3.121	0.469 ± 0.503
Sucker	35	0.02 - 0.37	0.140 ± 0.08
Walleye	59	0.036 - 1.428	0.458 ± 0.323

Similar trends were observed between log-transformed fish tissue HgT concentration and wet weight. Whether represented as EPA+DHA, EPA+DHA+DPA, total omega-3 PUFAs, or total PUFAs, there were substantial differences in fatty acid profiles among fish species (**Table 4-2**). For example, EPA+DHA concentrations in Lake Trout were up to 4.5 times higher than observed in other piscivorous fish species harvested, including Burbot, Northern Pike, and Walleye (**Table 4-2**). Furthermore, Lake Trout demonstrated total PUFA concentrations that were 5.2 times higher than of those observed in Burbot, 3.3-fold higher than in Northern Pike, and 3.0-fold higher than in Walleye (**Table 4-2**). Lake Whitefish, the most commonly consumed fish in the Dehcho region (Receveur et al., 1996), had total omega-3 PUFA levels that were up to 3.6 times higher than the average levels observed in Northern Pike, Burbot and Walleye (**Table 4-2**). When examining species-based lipid concentrations in descending order, Lake Trout

demonstrated the highest fatty acid levels, followed by Burbot, Cisco, Lake Whitefish, Northern Pike, Sucker, and Walleye (**Table 4-2**). Interestingly, this species order was observed for DHA, EPA+DHA, EPA+DHA+DPA, and total omega-3 PUFAs. A strikingly similar pattern was observed for total PUFAs; however, for this fatty acid grouping, Sucker had slightly higher levels than Lake Whitefish. The consistent ranking order of species is not entirely surprising, given the strong correlations between lipid groups that were examined in this analysis.

Mean HgT concentrations differed significantly between lakes for Lake Whitefish (ANCOVA, F=46.38, P<.0001, df=15,84) and Walleye (ANCOVA, F=25.29, P<.0001, df=11,58), however, when compared among lakes with an ANCOVA, the interaction between lake and fork length was significant. Pairwise comparisons indicated that Lake Whitefish harvested from Tathlina Lake and Gargan Lake were significantly higher than those harvested from Trout Lake and Kakisa Lake, while Walleye harvested in McGill and Tathlina Lake were significantly higher than those harvested in Ekali, Trout, and Kakisa Lake (Tukey's test, P<0.05). Total HgT in Lake Trout did not appear to differ significantly across lakes, after standardization to a common size (LSMEANS HgT at 650 mm length, ww; ANCOVA, F=17.14, P=0.33, df=3,50). Total HgT concentrations in Northern Pike differed across significantly across lakes, after standardization to a common size (LSMEANS HgT at 450 mm length, ww; ANCOVA, F=46.38, P<.0001, df=15,84).

Pairwise comparisons of length-adjusted mean HgT concentrations indicated that Northern Pike in Sanguez Lake, McGill Lake, and Ekali Lake had significantly higher HgT levels than those found in other lakes, while Northern Pike harvested from Trout Lake and Mustard Lake had significantly lower mean HgT relative to other lakes (Tukey's test, P<0.05). Average HgT concentrations fell below the 0.5 µg/g guideline in each lake for Burbot, Cisco,

Lake Trout, Lake Whitefish, and Sucker. In contrast, although the overall mean HgT concentration in Northern Pike fell under the 0.5 μg/g guideline (**Table 4-1**), this was not the case for Northern Pike in Sanguez Lake (**Supplementary Table A1**). The arithmetic mean tissue mercury concentrations for Walleye exceeded the 0.5 μg/g guideline in Sanguez Lake, McGill Lake, and Tathlina Lake (**Supplementary Table A1**).

Substantial differences in fatty acid composition were also noted among lakes in some species harvested (**Supplementary Table A2a, Supplementary Table A2b**). For example, total PUFAs in Lake Trout from Trout Lake were 3.7-fold higher than from fish harvested in Mustard Lake. Additionally, Sucker harvested from Tathlina Lake was demonstrated to have tissue PUFA levels up to 2.8-fold higher than in other lakes. Total PUFA levels from Lake Whitefish harvested from Sanguez Lake appeared to be up to 3.7 times higher than in other lakes, although this was largely attributed to one outlier among the Lake Whitefish samples from Sanguez Lake (**Supplementary Figure A1d**).

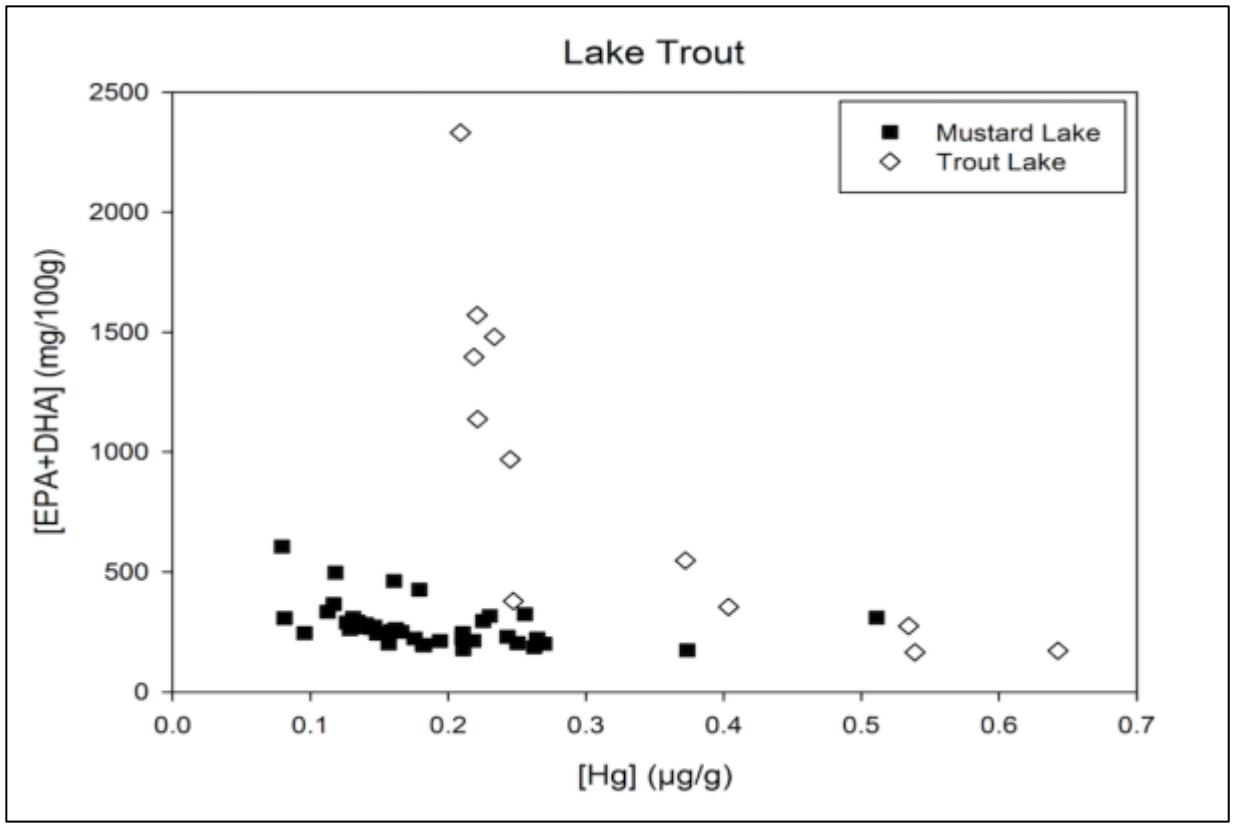


Figure 4-1. Relationship between mercury and EPA+DHA concentration in Lake Trout caught in Mustard Lake and Trout Lake.

Table 4-2. Fatty acid profiles of fish harvested in the Dehcho region, Northwest Territories, Canada (2013, 2014, 2015).

Species	N=333	EPA+DHA (mg/100 g)		EPA+DHA+DPA (mg/100g)		Total omega-3s (mg/100g)		Total PUFAs (mg/100g)		N-6/N-3 Ratio	
		Range	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD
Burbot	14	57 - 128	94 ± 19	62 - 143	104 ± 22	68 - 149	111 ± 22	109 - 255	177 ± 44	0.45 - 0.80	0.59 ± 0.14
Cisco	21	145 - 380	235 ± 61	158 - 439	259 ± 71	187 - 693	351 ± 123	252 - 935	458 ± 167	0.24 - 0.41	0.30 ± 0.05
Lake Trout	51	165 - 2332	424 ± 428	186 - 2813	505 ± 517	193 - 4247	662 ± 788	267 - 5570	916 ± 1036	0.28 - 0.71	0.40 ± 0.10
Lake Whitefish	68	182 - 1048	288 ± 122	195 - 1223	320 ± 142	212 - 2050	401 ± 248	281 - 3145	573 ± 384	0.22 - 0.66	0.41 ± 0.10
Northern Pike	85	100 - 707	181 ± 88	108 - 758	197 ± 96	115 - 835	214 ± 107	166 - 1094	291 ± 142	0.20 - 0.61	0.37 ± 0.08
Sucker	35	87 - 807	194 ± 117	96 - 856	211 ± 126	112 - 909	229 ± 137	162 - 1197	312 ± 182	0.25 - 0.73	0.47 ± 0.11
Walleye	59	148 - 589	262 ± 89	164 - 723	301 ± 112	170 - 1064	386 ± 195	253 - 1733	581 ± 339	0.21 - 0.62	0.37 ± 0.08

Lake-specific differences between fatty acid groupings and total fatty acids in fish tissue were also noted (**Supplementary Table A4**). EPA+DHA in the tissues of Lake Trout harvested from Mustard Lake contributed to 22% of all fatty acids, compared to only 16% in Trout Lake, despite being 3.2-fold greater in Trout Lake as compared to Mustard Lake. Similarly, EPA+DHA levels from White Sucker harvested from Tathlina Lake contributed to 14%, whereas EPA+DHA from fish harvested from McGill Lake contributed to 30%, despite levels of EPA+DHA being 4.1-fold greater in Tathlina Lake.

4.3.2 Correlations Between Fatty Acids and Mercury

Significant negative Spearman rank correlations were observed between mercury and fatty acid content for predatory species, specifically Burbot, Northern Pike and Walleye (**Supplementary Table A3**). Particularly strong negative relationships were observed between HgT and omega-3 PUFA content for Burbot (ρ = -0.670, P=0.0087), Northern Pike (ρ = -0.479, P<0.0001), and Walleye (ρ = -0.446, P=0.0004) (**Supplementary Table A3**). When pooling results across lakes, for Cisco, Lake Trout, Lake Whitefish, and Suckers, no meaningful relationships were observed between Hg and fatty acid content. Interestingly, Suckers were the only species to show a positive, albeit statistically insignificant, association between Hg and all fatty acid groupings.

Stratifying results by lake revealed a series of lake-specific differences in the associations between mercury and fatty acid content where the relationship was significant for some but not all fatty acid groupings. For example, Walleye harvested from Kakisa Lake demonstrated a strong negative relationship between EPA+DHA and Hg, but not between Hg and total PUFAs nor Hg and total omega-3 PUFAs (**Supplementary Table A3**). Similarly, Cisco harvested in Kakisa demonstrated strong negative relationships between Hg and total omega-3 PUFAs and

Hg and total PUFAs, but not with EPA+DHA or EPA+DHA+DPA. Also, among Lake Whitefish from Gargan Lake, a strong negative relationship was observed between Hg and total omega-3 PUFAs, but not with other fatty acid groupings. In contrast, Sucker from Kakisa Lake demonstrated strong negative relationships between Hg and all fatty acid groups.

The lake-stratified results were particularly interesting for Lake Trout. Specifically, when results were pooled across lakes, no relationships were seen between Hg and fatty acid content in Lake Trout (ρ = -0.182, P=0.200). However, when further grouped by lake, strong negative correlations were observed between Hg and EPA+DHA for Lake Trout from Trout Lake and Mustard Lake (**Figure 4-1**).

4.3.3 Fatty Acid:Mercury Ratios

As with fatty acid and HgT content in fish muscle tissue, fatty acid:mercury ratios varied by lake and species. Stratifying by species, the overall arithmetic mean DHA:HgT ratios for Lake Whitefish and Cisco were up to 8.7-fold higher than in Northern Pike, Walleye and Burbot (**Supplementary Table A4**). Generally, piscivorous species demonstrated low fatty acid:mercury ratios. However, as they are particularly rich in several healthy fats, the main exception to this trend was Lake Trout. Cisco, Lake Trout, Lake Whitefish, and Sucker exceeded the established *de minimus* ratios for DHA:HgT (15 mg:1 µg) and EPA+DHA:HgT (19 mg:1 µg) (**Figure 4-2**).

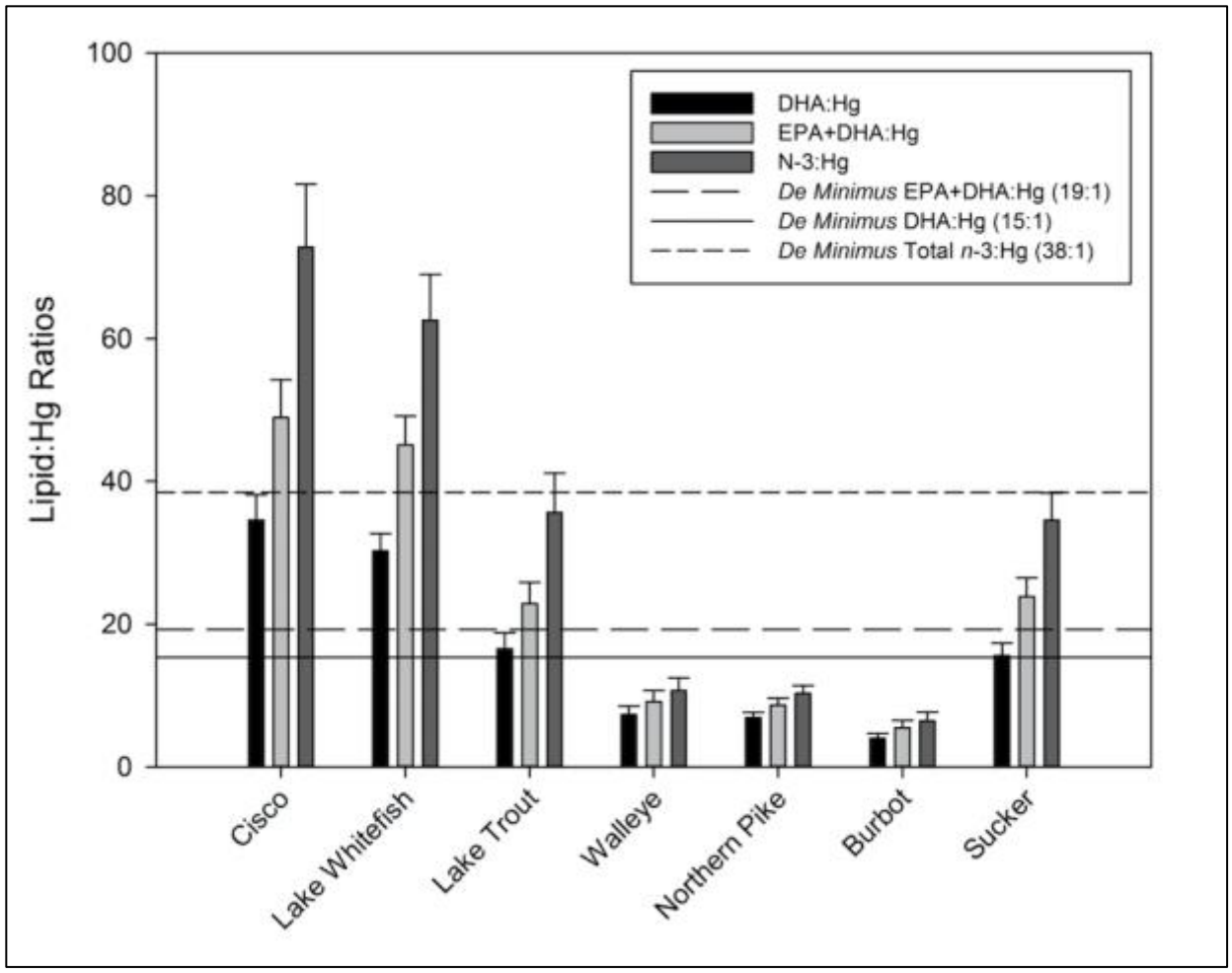


Figure 4-2. Mean Fatty acid:mercury ratios ± standard error for fish species harvested in freshwater lakes of the Mackenzie Valley Region, Northwest Territories, Canada, as compared with the *de minimus* ratio established using Health Canada guidelines for fish tissue Hg.

However, only Cisco and Lake Whitefish exceeded the *de minimus* ratio of 38 mg:1 µg ratio for total omega-3 PUFA:HgT. Burbot, Northern Pike, and Walleye fell below the *de minimus* ratios for all three fatty acid groupings (**Figure 4-2**). Stratifying by lake, fatty acid:mercury ratios were observed to vary significantly within species depending on where the fish were sampled. Lake Trout harvested from Trout Lake demonstrated DHA:HgT ratios that were 2.3-fold higher than those sampled in Mustard Lake. Similarly, DHA:HgT ratios for Walleye harvested from Trout Lake were demonstrated to be up to 10.6-fold higher than in other lakes (**Supplementary Table A4**). Generally, across all fatty acid groupings, McGill, Sanguez,

and Tathlina Lakes were observed to rank consistently in containing fish with the lowest fatty acid:mercury ratios, and were most likely to fall below the established *de minimus* value.

4.4 Discussion

This study contributed to the consolidation and characterization of mercury and omega-3 PUFA concentration profiles in wild-harvested freshwater fish species of the lakes in the Dehcho region of the Mackenzie Valley in the Northwest Territories. Building off of work conducted by Reyes et al., this study provided lake- and species-specific data for HgT and fatty acid profiles in fish species (Reyes et al., 2017). Consistent with previous studies, elevated mercury concentrations were demonstrated to be common in predatory fish species harvested in lakes of the Mackenzie Valley, and fish size was strongly associated with mercury content in fish tissue (Reyes et al., 2017). Furthermore, while species- and lake-specific differences in fatty acids highlight significant disparities in fatty acid quantity between lakes, further examining the relative percent contribution of an important fatty acid grouping (e.g. EPA+DHA) to the total fatty acids in fish tissue ultimately reveals differences in fish fat quality. This is important to note and future studies might benefit from exploring the factors that contribute to variation in relative percent contribution.

In response to earlier studies highlighting the presence of elevated Hg concentrations in the tissues of several fish species harvested in the Dehcho region (Evans et al., 2005; Lockhart et al., 2005), the Northwest Territories Department of Health and Social Services (DHSS) released a series of fish consumption notices (DHSS, 2016). These consumption notices were created and released by the DHSS using the results of previous studies characterizing levels of mercury in fish caught in the Northwest Territories. The latest fish consumption notices published for the

Dehcho region include advisories for Ekali Lake, Gargan Lake, McGill Lake, Sanguez Lake, Tathlina Lake, and Trout Lake, along with several others which were not sampled in the scope of this work (DHSS, 2016). These consumption notices were issued to help communities and individuals limit their contaminant exposure while still promoting the benefits of country foods.

Local fish consumption notices stated that predatory fish in the Dehcho are generally safe to eat occasionally. However, due to the bioaccumulative nature of mercury, consumers should choose smaller fish whenever possible. Consumption notices for Northern Pike (including those for Tathlina, Ekali, and Sanguez lakes) stipulated that the occasional consumption of this species was not harmful, however the DHSS recommended restrictions of 2 servings/month for pregnant or breastfeeding women. Also, people consuming Northern Pike harvested from McGill Lake were advised to avoid or limit the consumption of fish >74 cm, while fish between 43 and 74 cm could be consumed occasionally, and those <43 cm were safe to consume on a regular basis.

In subsistence cultures such as the First Nations communities of the Dehcho region in the Mackenzie Valley basin, the presence of mercury and other environmental contaminants in traditional food systems can potentially pose noteworthy public health risks. That being said, the nutrients in fish, including EPA, DHA, and other long-chain PUFAs, yield population health benefits that are of particular significance to communities where these nutrients are harder to come by due to the limited range of market foods available (Gagné et al., 2012). Northern First Nations communities are experiencing a gradual, generational and cultural shift away from locally-harvested food sources, concurrently increasing their consumption of energy-dense, less nutritious store-bought foods (Seabert et al., 2014). This transitional shift represents a decline in diet quality and nutritional status, and along with other lifestyle changes including reduced physical activity is a major potential contributor to the growing prevalence of chronic disease

including diabetes and CVD (Kuhnlein and Receveur, 1996; Gagné et al., 2012). Care must continue to be taken to ensure that consumption notices do not enforce a stigma among subarctic First Nations communities against eating traditionally harvested food. In particular, messaging must continue to be framed such that risk communication strategies do not lead to a general decline in fish consumption among these populations (Oken et al., 2003; Cohen et al., 2005).

Public health strategies, consumption notices and interventions that are adopted in subarctic First Nations communities must continue to consider the potentially harmful cultural and nutritional implications of framing these dietary staples in overly negative contexts. A series of quantitative measures have been proposed with the aim of generating a balanced message to promote healthy fish consumption and minimize contaminant intake. A study conducted by Ginsberg and Toal (2009) incorporated a multivariate approach to the risk-benefit analysis of methylmercury exposure from fish consumption. This work involved constructing dose-response relationships for omega-3 PUFAs and MeHg for common health outcomes, including cardiovascular disease in adults and neurodevelopment in 6-month old infants. Their quantitative analysis of both the risks and health benefits of consuming fish and fish oils represents an integrated assessment of the net effect of fish consumption on a species basis, and could serve as a framework to establish advisories for commercially available and locally harvested fish when omega-3 PUFA and MeHg contaminant profiles are available. A similar methodology was used in a study conducted by Cohen et al. (2005), which examined the change in relative risk on incremental CHD mortality risk, stroke risk, and potential changes in IQ for women of childbearing age from dietary modifications to fish consumption. Their work underscored the importance of bearing in mind the potential adverse effects of efforts to communicate MeHg risks from fish consumption. Specifically, that a target audience may reduce their consumption

of highly nutrient-dense foods, when in fact the risks posed by MeHg on their health are relatively low (Cohen et al., 2005).

Seabert et al., (2014) conducted a community-specific cross-sectional analysis of contaminant and total PUFA profiles in Northern Boreal First Nations communities, comparing consumption patterns to risks and benefits of dietary wild-harvested fish consumption. In participants whose diet comprised a relatively greater proportion of country foods, they observed higher levels of persistent organic pollutants (POPs) and mercury than in participants who consumed these foods less frequently, many participants who frequently consumed country foods exceeded recommended intake limits for methylmercury and polychlorinated biphenyls (PCBs). However, those consuming more wild-harvested foods had correspondingly higher proportions of total PUFAs. Their study adopted an approach to quantifying the risks and benefits of consuming country foods by pairing human exposure data with consumption patterns in Northern First Nations communities, and revealed the importance of considering the benefits of traditional food systems within regional, sociocultural and environmental contexts.

The *de minimus* approach used herein provides a preliminary means of establishing which species may be the best to eat when considering both the nutritional benefits and toxicological risks of food choices. For example, fatty acid:mercury ratios were highest among planktivorous species including Cisco, Lake Whitefish, and Sucker – each of which were generally higher than the *de minimus* reference ratios established for each fatty acid grouping (**Figure 4-2**). In contrast, Burbot, Northern Pike and Walleye demonstrated considerably lower fatty acid:mercury ratios. Lake Trout was the one piscivorous species which often met or exceeded *de minimus* ratios based on fatty acid content (**Figure 4-2**). However, stratifying by lake revealed significant differences in fatty acid content, mercury levels, and fatty acid:mercury

ratios within species, demonstrating that the balance of nutritional benefits and potentials risks from mercury can vary considerably from one lake to another (**Supplementary Table A4**).

Generally speaking, the results of this *de minimus* approach are in agreement with current consumption notices for fish species in the Northwest Territories (DHSS, 2016). In species that demonstrated fatty acid:mercury ratios that typically fell below the relevant established *de minimus* value, consumption notices were often posted for lakes where these species demonstrated particularly low fatty acid:mercury values. These notices caution against the consumption of fish above a given fork length, and outline a frequency by which the fish can be safely consumed. When ranked by fork length, all Lake Trout samples that exceeded the 0.5 μg/g standard outlined by Health Canada had a fork length greater than 60 cm. Similarly, mean DHA:HgT ratios among Lake Trout harvested in Trout Lake less than 60 cm in length were demonstrated to be 3.1-fold higher than in those fish that were greater than 60 cm in length. In contrast, in species that consistently demonstrated fatty acid:mercury ratios exceeding the relevant *de minimus* value, the same consumption notices typically outline that these species can be consumed at one's discretion, and that the nutritional benefits of regularly consuming these species outweighs the risks posed to human health.

There are notable limitations to the *de minimus* approach to consider. For example, the ratios reported in this work considers only the independent benefits of DHA, EPA+DHA, or total omega-3 PUFAs, without considering the contributions of other nutrients in an integrative approach. Similarly, HgT is the only contaminant considered within the scope of this assessment; other potential contaminant risks are not characterized. Further, the derivation of *de minimus* ratios assume a uniform fish intake:body weight ratio; the validity of the assumption within this population is not yet known. Additionally, dietary lipid recommendations vary widely by

regulatory agency; this introduces uncertainty in the *de minimus* calculations. Furthermore, the *de minimus* approach applied in this study assumed that fish Hg was entirely present as methylmercury. Although a generally reasonable presumption (e.g. methylmercury is likely to drive mercury risks from fish consumption; fish mercury is commonly 95% methylmercury) (Bloom, 1992), fish samples occasionally contain substantial fractions of inorganic mercury as a result of internal demethylation and elimination mechanisms (Bloom, 1992). Speciation analyses of the mercury in fish tissues would help clarify this source of uncertainty. Finally, this *de minimus* approach adopted a series of toxicological reference values and dietary reference intakes that are most applicable to women of child-bearing age, thereby limiting the generalizability of this approach to other demographics. In particular, the *de minimus* ratios reported herein may be overly conservative for the general adult population.

4.5 Conclusion

The inherent sociocultural, spiritual, and nutritional benefits of wild-harvested country food consumption must be carefully taken into account when defining the risks associated with dietary exposure to mercury, and any public health messaging and interventions that define these risks, especially among subarctic indigenous populations, must be predicated upon a more holistic assessment. While including several fatty acid groupings within the *de minimus* approach described in this study provides a more nuanced assessment than generated in similar previous studies (Reyes et al., 2017), future studies would benefit from a framework that simultaneously integrates results from multiple contaminants and nutrients. Furthermore, while *de minimus* values provide a preliminary means of evaluating species- and lake-specific nutrient:contaminant ratios, it is important to remember that these ratios are subject to the uncertainty within the

nutritional and toxicological reference values used in their derivation. As such, it would be inappropriate to treat *de minimus* ratios as a clearly defined evaluation of net benefit and net risk. This issue is compounded by the fact that a particular set of samples can exceed the *de minimus* ratio for one fatty acid group (e.g. EPA+DHA), but not for another (e.g. total omega-3 PUFAs).

Probabilistic approaches to assessing contaminant and nutrient intake can be a viable and effective tool in risk-benefit assessment, to estimate the proportion of a population that may exceed an established reference value for contaminant exposure and/or fall below the suggested daily intake of one or more nutrients (Hellberg et al., 2012). Several studies have explored the utility of exposure assessment models in characterizing contaminant and nutrient intakes from the consumption of fish and other seafood (Cohen et al., 2005; Cardoso et al., 2010). By simultaneously modeling exposure to both contaminants and nutrients in fish consumed by the population, probabilistic dose reconstruction models can allow researchers to characterize changes in intakes to both nutrients and contaminants in response to changes in dietary patterns (van der Voet et al., 2007). Probabilistic models are better able to account for the variability and uncertainty inherent within data than deterministic models, and are useful tools for the characterization of the risks and benefits of seafood consumption (van der Voet et al., 2007).

The Spearman rank correlations presented herein (Supplementary Table S6) are key input parameters for the development of probabilistic models that will help identify which traditional food choices best help individuals and communities improve nutritional status while limiting contaminant exposure among subarctic First Nations communities. As only a subset of lakes from which fish are consumed could be sampled for these types of analyses, a general understanding of the patterns of fish fatty acid and mercury profiles across species is important. For example, the tendency of predatory fish to demonstrate higher mercury content than non-

piscivorous fish has formed the basis of the General Fish Consumption Guidelines released by the Government of the Northwest Territories[35]. In contrast, the fatty acid composition of Lake Trout from Mustard Lake was similar to that observed in other species and lakes while Lake Trout from Trout Lake showed significantly different patterns. These observations underscore the importance of: i) incorporating lake-based differences into site-specific exposure and risk characterisation; and ii) the collection of Lake Trout from additional lakes in order to obtain a clearer picture of the most typical fatty acid profile(s) for this species.

This work provides the largest composite dataset of paired mercury and omega-3 PUFA profiles in fish harvested from lakes of the Canadian subarctic. Further, the species considered within the scope of this work encompass the majority of locally-caught fish harvested by Indigenous fishers in the region, and were identified by community partners to be of significant priority. This research, which serves as an up-to-date analysis of fish mercury profiles in lakes of the Dehcho, contributes to an improved understanding of increasing Hg levels in particular lakes of the Mackenzie Valley. Co-located with a comprehensive biomonitoring study currently ongoing in communities of the Dehcho, this work will further inform the development of geographically relevant consumption notices to better guide public decision making, and will facilitate the assessment of risks and benefits from locally harvested fish consumption. Altogether, this research is helping to guide risk communication strategies and promote the development of messages that aim to maximise traditional food use, and minimise contaminant exposures in First Nations communities of the Dehcho region.

5. Probabilistic Modeling of Exposure to Mercury in the Dehcho Region of the Mackenzie Valley, Northwest Territories: The Contaminants Biomonitoring Study

5.1 Introduction

Country food consumption contributes significant social, cultural and health benefits to First Nations communities of the Canadian subarctic, and promotes sociocultural autonomy, sovereignty, and improved food security (Kuhnlein and Receveur, 2007). These country foods represent the inherent and intricate relationship of First Nations peoples with the land and consequently with the surrounding ecosystems that have historically played an important role in the cultural identity, preservation and wellbeing of Northern First Nations communities. Locally wild-harvested fish species are widely recognized as healthy food choices in these communities, providing an excellent source of protein, long-chain omega-3 polyunsaturated fatty acids (PUFAs), and other essential micronutrients (Kuhnlein and Chan, 2000; Kuhnlein et al., 2006; Reyes et al., 2016). Omega-3 PUFAs have been demonstrated to contribute to improved fetal neurocognitive and retinal development, reduced risk for coronary heart disease and other cardioprotective properties, and a role in anti-inflammatory processes. Studies have also demonstrated the role of omega-3 PUFA intake in contributing to healthy ageing, while a diet deficient in omega-3 PUFA intake is considered to be associated with poor fetal development, general cardiovascular health, and an increased risk for the development of Alzheimer's disease (Swanson et al., 2012).

Despite the range of nutritional benefits conferred through fish consumption, this food source can also present potential health risks. Mercury is well-known to have neurotoxic properties, and in particular can have significant detrimental neurocognitive impacts during *in*

utero development and in earlier stages of the lifespan. Exposure to mercury as methylmercury (MeHg) from fish continues to present a significant public health concern. The majority of human exposure to MeHg occurs primarily through fish and seafood consumption (Forsyth et al., 2004), and at high doses this contaminant is a well-known and widespread neurotoxicant that is easily and almost entirely absorbed in the gastrointestinal tract, with the ability to readily cross placental and blood-brain barriers (Clarkson, 2002). However, as the portion of total mercury present as methylmercury has been determined to vary significantly between species, no fixed conversion factor could accurately estimate actual levels of MeHg in fish tissue. For this reason, Canadian human health risk assessors conservatively assume that all mercury ingested through fish consumption is present as MeHg (Forsyth et al., 2004).

In order to protect and mitigate the risks associated with methylmercury exposure, Health Canada adopted a series of biomonitoring guidance values and public health recommendations that specifically address the risks of mercury as they manifests by age, sex, and level of exposure. To identify individuals considered to be at risk, the First Nations and Inuit Health Branch of Health Canada established guidance values for methylmercury based on recommendations made by the World Health Organization (WHO)'s Joint Expert Committee on Food Additives in 1972 (JECFA, 1972). The TWI, which was based on findings from largescale incidents of methylmercury exposure in Japan and Iraq, was adopted by Health Canada's Food Directorate and expressed as the provisional Tolerable Daily Intake (pTDI) of 0.47 μg/kg/day (or 3.29 μg/kg/week) for the general population. Later, in response to findings from two prospective epidemiological studies investigating the effects of chronic low level prenatal MeHg exposure conducted in the Seychelles and Faroe Islands, Health Canada further developed and refined a pTDI of 0.20 μg/kg/day for pregnant women, women of childbearing age, and infants and young

children, in order to reflect the unique susceptibility in these sensitive subgroups of the population.

The Omega-3 Index is an indicator proposed by Harris and von Schacky (2004) to fulfill the criteria for a novel cardiovascular risk factor, and is a tool used to quantify population-level cardioprotective benefits of omega-3 PUFA consumption through blood levels of EPA+DHA (Harris and Von Schacky, 2004; von Schacky, 2014). Because red blood cell membranes (RBCs) reflect cardiac membrane omega-3 PUFA content, it was proposed that the content of EPA and DHA in RBC membranes (which are expressed as a percent of total fatty acids) be considered a new risk factor for death from CHD (Harris and Von Schacky, 2004). By compiling a summary of clinical and laboratory evidence from studies examining the relationship between measures for blood omega-3 PUFAs and risk for death from coronary heart disease (CHD), the Omega-3 Index was proposed as a validated, modifiable risk factor for death from CHD, and served as a measure in other work to gauge the cardioprotective benefits of omega-3 PUFAs across populations (Stark et al., 2016b).

Human biomonitoring investigations are key tools implemented as a quantitative measure to provide baseline data on environmental exposure to chemicals or contaminants. At the national level, the Canadian Health Measures Survey is the most comprehensive health measures survey conducted in Canada, and includes a detailed human biomonitoring component to characterize profiles of exposure among the Canadian population to environmental chemicals through urine and blood analyses. Depending on the contaminant of interest, and given the option to assess these profiles of exposure through less invasive tissue, human biomonitoring studies also employ the use other media, including human hair, to gauge exposure. Hair is

commonly used as an indicator to profile mercury exposure due to its non-invasive nature, and can be segmented to characterize temporal exposure (Grandjean et al., 1999).

While the CHMS characterizes the health of the Canadian general population, it does not include First Nations peoples living on-reserve. Furthermore, for subpopulations wherein fish and marine species are consumed in relatively higher quantities, and specifically among demographics where these foods are part of traditional food systems, it is important to highlight how these dietary patterns may disproportionately influence mercury intake among remote Indigenous communities. In an effort to generate nationally-representative results and baseline data characterizing human exposure to environmental contaminants for First Nations living on-reserve, the First Nation Biomonitoring Initiative (FNBI) was designed as a survey to complement the results of the CHMS. In 2011, after the pilot year of the study, the First Nation Biomonitoring Initiative (FNBI) found blood mercury levels in First Nations to be, on a national average, similar to those reported from the general population through the CHMS. However, while the FNBI pioneered the first biomonitoring survey to represent focused research and priority to understanding contaminants exposure in First Nations communities on a national scale, the scope of this survey included only the 10 provinces, and not the Northern Canadian territories. The First Nations Food, Nutrition, and Environment Study has characterized provincial-level baseline data on the composition, quality and profiles of exposure to environmental contaminants through the diets of First Nations peoples, with a specific focus on country foods (Chan et al., 2014). However, there is a distinct need to identify and characterize contaminant exposure among subarctic First Nations populations, for whom the role of country foods in contributing to this exposure is uncertain (Receveur et al., 1998).

In response to studies investigating elevated mercury exposure in fish species native to lakes of the Dehcho region in the Mackenzie Valley, Northwest Territories, the Government of the Northwest Territories Department of Health and Social Services developed and released a series of fish consumption notices to advise consumers of the risks and benefits associated with consuming certain species of locally harvested fish in different quantities (DHSS, 2016). As fish consumption confers both benefits and risks, any risk management or communication could introduce the possibility of a trade-off wherein consumers of traditionally harvested fish incur potentially adverse health consequences associated with low omega-3 PUFA intake in order to lower their exposure to MeHg (Cohen et al., 2005; Shimshack and Ward, 2010). As demonstrated by Cohen et al. (2005), individuals who reduce their fish consumption in response to national recommendations can demonstrate a negative net health impact. The balance between risk and benefit, and the potential pitfalls of lowering fish consumption in response to published dietary recommendations, are of particular importance in subarctic First Nations populations, where country foods contribute inherently to cultural and spiritual identity and sovereignty, and where food security is a more pressing concern in remote indigenous communities than in other parts of the country. Furthermore, diet is a key contributing factor to many health outcomes, including diabetes, obesity, kidney disease, and cardiovascular disease, that have been found to be significantly more prevalent among First Nations peoples than in the general population (Dyck et al., 2010; Ashton et al., 2011; Tjepkema et al., 2012). Lower consumption of country foods has been associated with an increased risk of obesity (Kuhnlein et al., 2004), and the regular consumption of these foods is thought to beneficially influence cardiovascular disease risk factors (Dewailly et al., 2001). On a national scale, First Nations communities are experiencing a profound dietary transition shifting away from the use of country foods towards

imported market foods, which are often of lower nutritional quality. As country foods are often lower in saturated fats, simple carbohydrates, sodium, and sugars than market-based alternatives, dietary quality is significantly higher when locally-harvested country foods are regularly incorporated (Chan et al., 2014).

Effective risk communication is predicated upon informed risk benefit assessment, whereby risks and benefits are quantified simultaneously. Probabilistic exposure assessment can be an effective tool to jointly characterize the risks and benefits of fish and seafood consumption and identify patterns of exposure through the diet. Probabilistic exposure models allow for the estimation of the probability of a specific target population that is at risk of either exceeding or not meeting pre-established guidance values for contaminant exposure and nutrient intake, respectively. Probabilistic estimates of exposure address elements of variability within a given population, and allow decision-makers to identify and attempt to minimize both qualitative and quantitative uncertainty within the model.

This study utilized a retrospective probabilistic dose reconstruction model to simultaneously estimate mercury and omega-3 PUFA intake in First Nations communities of the Dehcho region of the Mackenzie Valley, Northwest Territories, by pairing nutrient and contaminant data from locally-harvested country foods with results from a multi-year contaminants biomonitoring project conducted in communities of the Dehcho. The objectives of this study were to: i) characterize and quantify sources of exposure to mercury and omega-3 PUFAs from country food consumption, and identify key contributing drivers of exposure from the diet; ii) assess the human health risk of methylmercury exposure within participating communities of the Dehcho through a probabilistic model; and iii) gauge the utility and accuracy

of the model at estimating population-level profiles of risk and cardioprotective benefit using biomarkers for omega-3 PUFAs in blood plasma and Hg in hair.

5.2 Methods

5.2.1 Participant Recruitment

The study design for the contaminants biomonitoring study has previously been described (Ratelle et al., 2017). Sample and data collection for the contaminants biomonitoring study was conducted in each of: January 2016 and November 2016 – February 2017, with a third and final sampling expedition planned for November 2017 – March 2018. While the contaminants biomonitoring study described herein is being run in both the Dehcho and Sáhtu regions, the current paper contains within its scope only participating communities sampled in the Dehcho within Years 1 and 2 of this research, so as to align with fish composition analyses described in Chapter 4. Local leaders, school officials, and hired local research coordinators helped to communicate the details of the study to residents of Jean Marie River, K'atl'odeeche First Nation, West Point, Fort Providence, and Ka'a'gee Tu First Nation, and informational documents were distributed to members of the community. Participant recruitment for each community was conducted several days prior to the commencement of the study. Within relatively small communities where the population size fell below 100 people (e.g. Jean Marie River, West Point, Ka'a'gee Tu), all community members were invited to participate. In contrast, in larger communities (e.g. K'atl'odeeche and Fort Providence), a random selection of households was selected and all community members within these households were invited to participate. Posters, radio broadcasts, personal invitations and phone calls to residents were among several means used to recruit community members. Among the larger communities, as

household demographics and resident details were not readily available, the average number of residents per household based on the total community population was used to estimate and assign an arbitrary number of households required to reach an expected participant ratio of 10%, and the equivalent of 40% of the population in each community was contacted. These participation rates were gauged and applied using the participation rates observed in the pilot community. All members of the community aged 6 years and older were eligible to participate, regardless of sex, family or parity status, or other characteristics.

Prior to participation, individuals were required to read through and sign a series of informed consent forms. Participants were given a thorough description of the study and its component parts, while it was emphasized that each participant was provided the choice to take part only in the project components with which they felt comfortable or interested. For any participant under 18 years of age, it was necessary to explain the project both to the minor and to their legal parent/guardian. The minor participant was required to provide their expressed verbal and written consent, while the parent/guardian was required to provide written consent for the minor. A translated copy of all recruitment and informational components were provided if required.

Ethics approval was received from the University of Waterloo (UW-ORE 20950) for the contaminant biomonitoring study in the Northwest Territories Mackenzie Valley. Furthermore, to satisfy all territorial ethics requirements, ethics approval was obtained from the Stanton Territorial Health Authority as well as research licenses from the Aurora Research Institute (Aurora Research Institute License 15775).

5.2.2 Dietary Assessment

Country food consumption in participants of the contaminants biomonitoring study over the preceding 12 months was quantified using a Food Frequency Questionnaire (FFQ) administered with face-to-face assistance, which has been described and implemented in past research (Jamieson et al., 2012; Labonté et al., 2012; Laird et al., 2013). Such FFQs are among the most commonly applied dietary assessment tools used to determine nutrient and contaminant intake among populations (Ferreira-Sae et al., 2009), and is particularly useful for research in Northern Indigenous Canadian populations (Pakseresht and Sharma, 2010).

The FFQ captured data pertaining only to participants' consumption of locally harvested country foods, and did not include self-reports of market food intake. All food selections offered in the FFQ had corresponding pictures of each species to ensure that country foods consumed were being accurately documented. These foods were further broken down, with information gathered on the parts of each food consumed and the methods of preparation used for each, as these factors may influence nutrient and contaminant exposure (Ouédraogo and Amyot, 2011; Neff et al., 2014). The FFQ questionnaire employed in participating communities of the Dehcho was based on similar tools used by Drs. Harriet Kuhnlein and Olivier Receveur for the Variance in Food Use in Dene/Métis Communities study, as well as other sources (Receveur et al., 1996; Hanning et al., 2009). Upon selecting a specific species, participants were prompted to outline the number of times per week that they typically consumed that particular food. A portion size document with images detailing a range of portion sizes was implemented in several communities where the biomonitoring study was conducted. After outlining the participants' typical portion size, this information was paired with FFQ data to evaluate weekly consumption frequency on a species-specific basis.

5.2.3 Collection of Hair

After obtaining informed consent from all participating individuals, trained research personnel cut out several hair strands from the occipital region of the scalp, as closely as possible to the root of the hair using sterilized stainless steel scissors. Hair strands were fastened to a sheet of paper with hair root directions (scalp and distal) clearly marked. For individuals with short hair, trimmings were taken from locations evenly distributed across the occipital region of the scalp, making sure to cut the hair as close to the scalp as possible. Hair samples were promptly sealed into polyethylene bag for later analysis, and collection and handling of samples were in accordance with previously established procedures (Chan et al., 2011).

5.2.4 Analysis of Total Mercury in Hair

Hair samples were weighed and introduced into the sample boat without any previous treatment. The sample was then wrapped in tinfoil, to minimize the risk of disturbance during analysis, and was introduced into the Direct Mercury Analyzer (DMA-80, Milestone®, Italy), where it was initially dried and then thermally decomposed in a continuous flow of oxygen. Combustion products were carried off and further decomposed in a hot catalyst bed. The detection limit was 0.005 ng of mercury. As part of quality assurance procedures, the standard reference material IAEA-086 (human hair, International Atomic Energy Agency, Austria) was analyzed after every tenth sample, and analysis continued only when the level of mercury in the reference sample was deemed acceptable. The analysis of HgT in hair followed procedures outlined by the U.S. Environmental Protection Agency (U.S. EPA) method 7473 (USEPA, 2000).

5.2.5 Collection of Blood

For participants who consented to providing a blood sample, a registered nurse hired through regional health authorities drew blood from the median antecubital vein of the anterior forearm with a 21G or 23G collection set (BD Eclipse™, Becton Dickinson, Rutherford, NJ). Blood samples were collected in metal-free plastic lavender 6 mL-vacutainer tubes containing K2EDTA (BD Vacutainer™, Becton Dickinson, Rutherford, NJ) for plasma analysis. Once collected, tubes of blood containing EDTA were centrifuged for 15 minutes at 3000 rpm in a portable centrifuge (VWR®, Mississauga, ON), separated in 1.2 mL polypropylene vials (Thermo Scientific™ Nalgene™, Waltham, MA) with disposable graduated transfer polyethylene pipettes (Fisherbrand™, Ottawa, ON), and stored below 4°C. Plasma vials pre-loaded with dibutylhydroxytoluene (BHT) were sent for fatty acid analysis to the laboratory of Dr. Ken Stark, Department of Kinesiology, University of Waterloo.

5.2.6 Analysis of Fatty Acids in Blood

Blood fatty acid profiling techniques closely followed procedures outlined in previous studies (Stark et al., 2016a). Total lipid extracts were prepared using a modified Folch protocol (Folch et al., 1957). In short, lipids in 50 µL aliquots of blood plasma were extracted using 3 mL of 2:1 chloroform-methanol (v/v) containing an internal standard (C22:3n-3 methyl ester). Samples were extracted by being vortexed vigorously for 1 min, adding 500 µL of 0.2 M $NaHPO_4$ buffer in ddH_2O (pH = 4.4), inverting twice and then centrifuging at 1734 *rcf* for 5 min to induce phase separation. The organic phase was collected, and an additional 2 mL of chloroform was added to the aqueous portion to facilitate a second lipid extraction. The second organic collection was added to the first and total lipid extracts were dried under a steady stream of liquid nitrogen (N_2). Fatty acid transesterification and FAME identification using fast-gas

chromatography of lipid extracts from plasma samples followed the same procedure as for fish samples outlined above.

5.2.7 Probabilistic Modeling of Exposure to Mercury and Omega-3 Fatty Acids

To characterize mercury and omega-3 fatty acid exposure from country foods consumed in the Dehcho region, a retrospective probabilistic dose reconstruction model was developed using Crystal Ball risk modeling software (version 11.1.2.4, Oracle® Crystal Ball, Fusion Edition, Oracle, USA). Probability distributions were fitted for all input variables. After performing a batch-fit analysis within Crystal Ball, continuous lognormal probability distributions were fitted to the Hg concentration profiles (in μg/g) for the seven species considered in the model. Similarly, lognormal distributions were fitted for fatty acid sub groups including DHA, EPA+DHA, total omega-3 PUFAs, and total PUFAs (in mg/g) using fatty acid profiles generated for the muscle tissue for each species.

Probability distributions for intake rate were modeled using species-specific consumption data generated from the FFQ, which represented the consumption frequency of the 7 different species considered in the model. As part of the survey, participants were asked to estimate their typical portion size using graphics that depicted a range of sizes of cooked fish. Across the study, median portion size was calculated to be 112.5 g/serving. This serving size was then used to extrapolate mean, minimum and maximum weekly estimated portions, which were used within the model to define probability distributions for fish intake rate. To account for non-consumers of the species of fish examined within this model, lognormally-modeled probability distributions for intake rate were paired with Bernoulli distributions generated in Crystal Ball. These distributions, which were based on the proportion of consumers among the total number of respondents in the FFQ, represented the probability of being a consumer for each species of fish

considered in the model. A probability distribution for body weight was also fitted using weight measurement data collected across the five participating Dehcho communities during the biomonitoring study. Minimum and maximum values for this distribution were assigned using 5^{th} and 95^{th} percentile truncation points, respectively.

Crystal Ball risk analysis software affords the opportunity to assign unique distributions to each input variable defined in the model. By characterizing the shape of each distribution using profiles of mercury and omega-3 PUFAs, as well as intake data and population characteristics from the contaminants biomonitoring study, it is possible to specify the relative probability that the model will generate values within the distribution. Probabilistic risk analysis addresses many of the deficiencies associated with single-point, deterministic models of exposure (Bogen et al., 2009). The Monte Carlo random sampling method is a viable approach used within probabilistic exposure assessments to address common deficiencies in the process of risk assessment and characterization, specifically overly conservative estimates of exposure (Burmaster and von Stackelberg, 1991; Paustenbach, 2000). Values were sampled at random from the assigned distribution curves in a series of 10,000 iterations using a two-dimensional Monte Carlo analysis. Sensitivity analyses were conducted to identify main drivers of the variance in the forecasts of interest, and potential key areas of uncertainty for which additional information may be needed to reduce uncertainty. Non-parametric Spearman's rank correlation coefficients characterize the association between input variables in the model. This included defining the relationship between mercury and fatty acid subgroups, as well as between fatty acids subgroups.

5.2.8 Forecast Variables

The forecast variables of interest outlined in this model included Total MeHg intake from each species (**Eq. 5-1**); total DHA intake from each species (**Eq. 5-2**); total EPA+DHA intake from each species (**Eq. 5-3**); total omega-3 PUFA intake (**Eq. 5-4**); total PUFA intake (**Eq. 5-5**); and total intake rate (g/week) (**Eq. 5-6**). Probability distributions were fitted for all forecast variables in the model, and Anderson Darling's goodness of fit test was used to assess the fit of these distributions. The forecast for total weekly methylmercury intake was standardized by bodyweight to facilitate comparison Health Canada's toxicological reference values (TRV) for this contaminant. In contrast, as Dietary Reference Intakes for the fatty acid subgroups included in this analysis are not standardized by bodyweight, all corresponding forecasts were calculated as mg per day. The mathematical equations used to compute these values are detailed below:

$$MeHg\ Intake\ (ug/kg/wk) = \frac{[[MeHg]\ (ug/g)\ X\ food\ (g/wk)]}{Body\ Weight\ (kg)} \quad \textbf{(Eq. 5-1)}$$

$$DHA\ Intake\ (mg/wk) = Fish\ (g/wk)\ X\ [DHA](mg/g) \quad \textbf{(Eq. 5-2)}$$

$$EPA + DHA\ Intake\ (mg/wk) = Fish\ (g/wk) X\ [EPA + DHA](mg/g) \quad \textbf{(Eq. 5-3)}$$

$$Omega - 3\ PUFA\ Intake(mg/wk) = Fish\ (g/wk)\ X\ [Omega - 3\ PUFAs](mg/g)$$

(Eq. 5-4)

$$Total\ PUFA\ Intake\ (mg/wk) = Fish\ (g/wk)\ X\ [Total\ PUFAs](mg/g) \quad \textbf{(Eq. 5-5)}$$

$$Total\ Intake = \Sigma\ Fish\ intake(g/wk) \quad \textbf{(Eq. 5-6)}$$

The model's performance and ability to effectively and accurately predict exposure among participating Dehcho communities was assessed by comparing forecasted estimates of exposure to total mercury and fatty acids generated in the model output to exposure profiles for hair mercury and fatty acid concentrations in blood from the human biomonitoring component of the contaminants biomonitoring study. Trials were sorted by weekly fatty acid consumption of

DHA, EPA+DHA, and omega-3 PUFAs, in order to determine the proportion that met dietary reference intakes (DRIs) for these subgroups (1,400 mg/week, 1,750 mg/week, and 3500 mg/week, respectively). The fatty acid estimates were then compared with biomarkers for omega-3 PUFA exposure from the results of the contaminants biomonitoring study, specifically the relative percentage of total fatty acids present as EPA+DHA in blood plasma. The Omega-3 Index for Dehcho participants of the contaminant biomonitoring study was computed and compared with patterns of fatty acid intake from the output of the probabilistic model, specifically the proportion of trials that met the relevant DRIs for fatty acid subgroups, where applicable.

Similarly, trials were sorted by total Hg intake, to determine and compare the proportion of trials that exceeded the pTWI for mercury with the proportion of participants from the contaminants biomonitoring study whose hair mercury profile exceeded Health Canada's recommended guidance value of 6 mg/kg (Legrand et al., 2010).

5.3 Results

5.3.1 Locally harvested fish consumption

As shown in Table 5-1, estimated intake rate varied by species. Forecasted estimates for mean consumption rate demonstrated that Lake Whitefish was the most frequently consumed fish in the Dehcho region, with a mean intake rate of 155 g/week. Predatory species, including Northern Pike (78 g/week), Walleye (55 g/week), and Lake Trout (51 g/week), followed as contributors to weekly fish consumption (**Table 5-1**). Comparatively, Sucker, Burbot, and Cisco contributed only 11% to the mean weekly intake of 379 g (**Table 5-1**).

Table 5-1. Estimated fish intake rate in g/week among 10,000 simulated trials from the output of the Crystal Ball model, and reported fish intake from the results of the FFQ (n=140). Reported fish intake reflects a median portion size of 112.5 g/serving of fish.

Intake Rate (g/week)	AM (SD)	GM	Percentile				
			5th	50th	75th	90th	95th
Estimated fish intake (g/week)							
Lake Whitefish	155 (144)	130	19	120	210	340	450
Northern Pike	78 (94)	100	0	54	120	210	270
Walleye	54 (84)	98	0	0	88	170	230
Lake Trout	51 (86)	69	0	10	71	150	220
Sucker	22 (45)	85	0	0	0	97	130
Burbot	14 (46)	75	0	0	0	48	100
Cisco	3 (22)	120	0	0	0	0	0
Total IR	**379 (220)**	**320**	**130**	**340**	**500**	**670**	**800**
Reported fish intake (g/week)							
Lake Whitefish	184 (182)	125	0	56			
Northern Pike	136 (109)	106	0	56	170	170	200
Walleye	126 (102)	99	0	0	56	170	170
Lake Trout	105 (115)	79	0	56	56	170	170
Sucker	102 (56)	88	0	0	0	56	170
Burbot	104 (95)	82	0	0	0	56	56
Cisco	141 (56)	128	0	0	0	0	0
Total IR	**416 (374)**	**283**	**0**	**230**	**560**	**890**	**1,100**

Measures of central tendency for forecasted weekly intake appear similar to those reported from the FFQ, however some discrepancies can be noted (**Table 5-1**). These discrepancies are due to the parameters used to derive the probability distributions for intake within the Crystal Ball model. Mean, minimum and maximum values for intake were selected and used to shape distributions on a species basis within the model. In contrast, the results from the FFQ shown in Table 5-1 depict more measures of central tendency and distribution than were used to define input variables for intake rate within the model.

The high mean estimated consumption rate of Lake Whitefish generated from the output of the model reflects the significant proportion of consumers of this species among the population. Results from the FFQ data indicated that 91% of the Dehcho population surveyed were consumers of Lake Whitefish muscle. Following Lake Whitefish, predatory fish including Northern Pike (60%), Lake Trout (51%), and Walleye (44%) were among the fish species consumed by the greatest proportion of the population within the Dehcho (**Table 5-2**).

Table 5-2. Consumption rates of wild-harvested fish species in the Dehcho population, in portions/week.

Species	% Consuming[a]	Mean portions/wk (SD)[b]	GM[b]	Percentile[b]				
				10th	50th	75th	90th	95th
Burbot	14	0.93 (0.85)	0.73	0.50	0.50	1.50	1.50	1.63
Cisco	03	1.25 (0.50)	1.14	0.80	1.50	1.50	1.50	1.50
Lake Trout	51	0.93 (1.03)	0.70	0.50	0.50	1.00	1.50	2.75
Lake Whitefish	91	1.6 (1.6)	1.11	0.50	1.50	1.50	4.00	5.75
Northern Pike	60	1.21 (0.97)	0.94	0.50	1.00	1.50	1.50	4.00
Sucker	23	0.91 (0.50)	0.78	0.50	0.50	1.50	1.50	1.50
Walleye	44	1.12 (0.91)	0.88	0.50	0.50	1.00	1.50	2.75

[a] The percentage listed only includes those participants who reported both consuming the fish species listed above, and gave a specific frequency of the food consumption (days/week). Those who listed themselves as consumers but who did not include further details were omitted.
[b] Represents mean intake among only consumers of the fish species (those who did not report consumption of the particular species are not represented in this value).

5.3.2 Population methylmercury exposure

Methylmercury exposure among the general population of the Dehcho region was modeled and estimated using MeHg exposure distributions created using Crystal Ball and simulated by Monte Carlo analysis using FFQ data collected during the biomonitoring study. These exposure distributions were compared to Health Canada's outlined pTWI for methylmercury of 3.29 µg/kg/week (**Table 5-3**).

Table 5-3. Primary contributors to MeHg exposure for the general population in the Dehcho region.

Fish	Mean Dose (µg/g/wk)	Mean Concentration (µg/g)	Mean Consumption Rate (g/wk)	% Consumers within the population
All trial values (n=10,000)				
Northern Pike	0.51	0.46	78	60
Walleye	0.35	0.45	55	44
Lake Whitefish	0.21	0.09	155	91
Lake Trout	0.17	0.23	51	51
Burbot	0.05	0.24	14	14
Sucker	0.05	0.14	22	24
Cisco	0.00	0.07	3.7	3
Total of All Fish	**1.33**	-	**379**	-
≥95th Percentile of MeHg Exposure (n=506)				
Northern Pike	3.00	1.01	189	88
Walleye	1.51	0.60	135	66
Lake Whitefish	0.33	0.10	179	92
Lake Trout	0.42	0.24	94	58
Burbot	0.10	0.25	22	17
Sucker	0.06	0.14	27	28
Cisco	0.00	0.07	2	2
Total of All Fish	**5.42**	-	**621**	-

This work demonstrated that average MeHg exposure among trial values fell below the established pTWI. However, the 95th percentile value for exposure estimates to MeHg exceeded this TRV of 3.29 µg/kg/week, with as many as 7% of trial values exceeded the pTWI overall (**Figure 5-1**). Of trial values that exceeded the pTWI for MeHg, 34% exceeded the Dietary Reference Intake for EPA+DHA of 250 mg/day, while 66% fell below the DRI. Among fish species incorporated within the scope of the model, Northern Pike (0.52 µg/g/wk) and Walleye (0.35 µg/g/wk) were the two primary contributors to weekly intake for MeHg (**Table 5-3**). While fish tissue mercury in the predatory species Lake Trout was demonstrated to be significantly greater than in Lake Whitefish, mean weekly MeHg intake from Lake Whitefish consumption (0.21 µg/g/wk) was 1.24-fold greater than from Lake Trout consumption (0.17 µg/g/wk). Combined, of the seven species considered in the model, predatory fish species including Northern Pike, Walleye, and Lake Trout contributed to 77% of the mean weekly MeHg intake among participating Dehcho communities (**Table 5-3**).

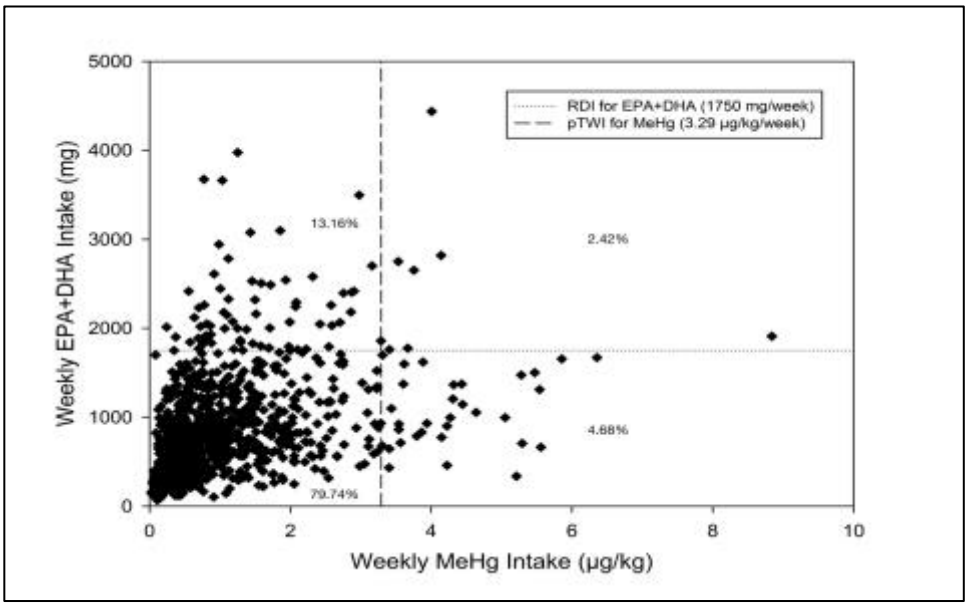


Figure 5-1. Modeling and estimating the simultaneous intake of EPA+DHA and MeHg among the Dehcho population. The vertical dashed line indicates the provisional Tolerable Weekly Intake (pTWI) for methylmercury of 3.29 µg/kg/week, while the horizontal dotted line corresponds to the Dietary Recommended Intake (DRI) for EPA+DHA of 1,750 mg/week.

Mean Hazard Quotient for MeHg exposure was calculated for the general population (0.41), and for the 95th percentile value for intake (1.10). For the purposes of human health risk assessment, an established HQ ≤ 1.0 is deemed to represent an acceptable or negligible risk. However, in terms of estimating risk according to the outlined quantitative level of conservatism (e.g. the 95th percentile value for exposure), Health Canada proposes that the 95th percentile dose estimate should have an HQ ≤ 1.0 (Health Canada, 2010a). The Hazard Quotient for those trials among the 95th percentile for exposure was observed to exceed 1.0 (0.41 ± 0.40) (**Table 5-4**), and 7% of iterations exceeded the pTWI for methylmercury (**Figure 5-2)**. However, according to the principles of a tiered risk assessment framework, before it is possible to ascertain whether current methylmercury exposure profiles pose a public health risk, it is important to revisit and evaluate the assumptions used to estimate population-level risk of exposure to consider whether these assumptions were overly conservative.

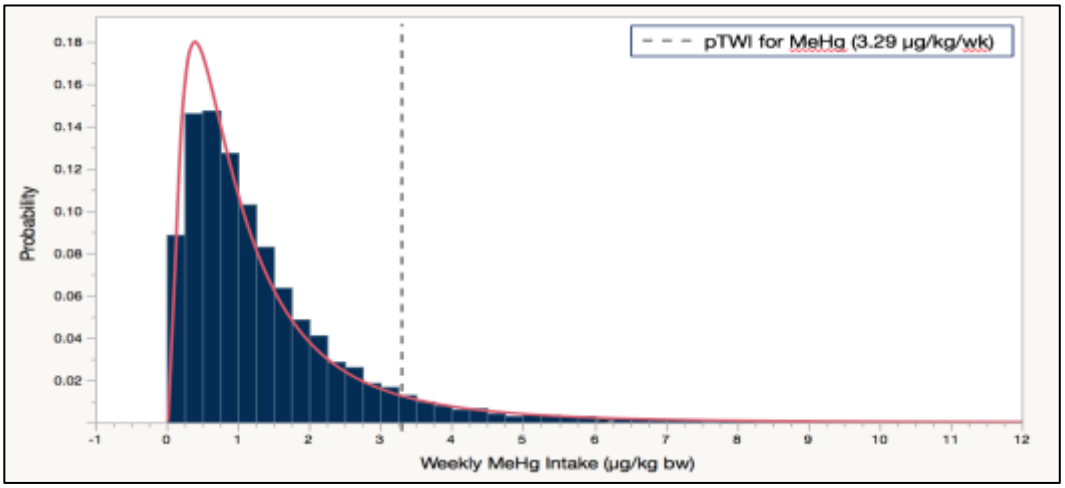


Figure 5-2. Estimated methylmercury (MeHg) intake among 10,000 simulated trials. The dashed line indicated Health Canada's pTWI for methylmercury of 3.29 µg/kg/week (based on the pTDI of 0.47 µg/kg/day.

Table 5-4. Probabilistic estimates for fatty acid intake and methylmercury exposure among the general population in the Dehcho (N=10,000).

Forecast Variable	Mean (SD)	GM	Percentile					%>TRV	Hazard Quotient[b]	%>DRI
			10th	50th	75th	90th	95th			
Total MeHg Dose (µg kg^{-1} wk^{-1})	1.33 (1.30)	0.88	0.23	0.97	1.70	2.82	3.74	7.1	0.4; 1.1	-
Total DHA Intake (mg wk^{-1})	792 (597)	621	241	654	1014	1480	1861	-	-	12
Total EPA+DHA Intake (mg wk^{-1})	1101 (823)	864	332	905	1414	2085	2594	-	-	16
Total omega-3 PUFA intake (mg wk^{-1})	1542 (1298)	1168	427	1210	1953	2997	3834	-	-	6.7
Total PUFA intake (mg wk^{-1})	2174 (1834)	1640	592	1707	2759	4257	5417	-	-	-

[a] Based on Health Canada's provisional Tolerable Weekly Intake of 3.29 µg/kg/week.

[b] Hazard Quotient: Mean; 95th Percentile

[c] Based on Dietary Reference Intakes for DHA (1,400 mg/week), EPA+DHA (1,750 mg/week), and omega-3 PUFAs (3,500 mg/week).

Further, human biomarker data can provide useful insight to compare and gauge the model's preliminary ability to characterize MeHg exposure among Dehcho participants, and clarify whether these assumptions may be illustrating conservative estimates of exposure.

Compared to hair profiles for Hg exposure from the contaminants biomonitoring study, the model's predictions for methylmercury intake appeared overly conservative. In contrast to the model's predicted estimates for dietary methylmercury exposure, for which 7% of trials were demonstrated to exceed the pTDI for MeHg intake, the vast majority of participants (i.e., 99.5%) had hair mercury results that fell below Health Canada's recommended hair guidance value of 6 mg/kg. Mean hair mercury was 0.74 mg/kg, with a geometric mean of 0.38 mg/kg (**Table 5-5)**.

Table 5-5. Hair mercury (in mg/kg) among participants of the contaminants biomonitoring study in the Dehcho region of the Mackenzie Valley, Northwest Territories (N=212).

	AM (SD)	Geo. Mean	Percentile				
			5th	50th	75th	90th	95th
Hair mercury (mg/kg)	0.74 (1.03)	0.38	0.06	0.44	0.87	1.71	2.20

5.3.3 Omega-3 PUFA intake

The nutritional content of the seven fish species considered in the model was reported in detail in Chapter 4, however model estimates for fatty acid profiles, and for weekly intake of DHA, EPA+DHA, omega-3 PUFAs, and total PUFAs can be found in Table 5-6. Among the species considered in the probabilistic model, Lake Whitefish was a predominant contributor to mean weekly intake for all fatty acid subgroups. Alone, this species contributed to 41% of DHA intake, 45% of EPA+DHA intake, 46% of omega-3 PUFA intake, and 47% of total PUFA intake (**Table 5-6**). Interestingly, Lake Trout was also a major contributor to total weekly intake across fatty acid subgroups, contributing to 25% for each of total DHA, omega-3 PUFA, and total PUFA intake, and 24% for EPA+DHA intake. While proportionately the respective contribution

of each species to the total intake for each fatty acid subgroup varied, the order in which these species fell in terms of increasing contribution remained consistent across all subgroups.

Table 5-6. Primary contributors to fatty acid exposure based on results provided by participants from five Dehcho communities.

Fish	DHA		EPA+DHA		Total omega-3s		Total PUFAs	
	Mean Dose (mg/wk)	**Mean Conc.** (mg/g)	**Mean Dose** (mg/wk)	**Mean Conc.** (mg/g)	**Mean Dose** (mg/wk)	**Mean Conc.** (mg/g)	**Mean Dose** (mg/wk)	**Mean Conc.** (mg/g)
Lake Whitefish	322	2.09	491	3.18	714	4.63	1019	6.61
Lake Trout	196	3.83	259	5.06	389	7.61	534	10.40
Northern Pike	125	1.61	155	1.61	183	2.35	251	3.23
Walleye	94	1.73	114	1.99	138	2.52	190	3.47
Sucker	38	1.71	61	2.70	90	4.02	138	6.18
Burbot	10	0.70	13	0.94	16	1.11	25	1.78
Cisco	6	1.69	9	2.39	13	3.58	18	4.73
Total	**792**		**1101**		**1542**		**2174**	

Forecasted mean and 50th percentile weekly intakes for all fatty acid subgroups (including DHA, EPA+DHA, and total omega-3 PUFAs) fell below the corresponding Dietary Recommended Intakes (**Table 5-4**). However, for weekly DHA intake, 12% of trials exceeded the DRI of 1,400 mg/week, while 16% of trial values exceeded the DRI for EPA+DHA of 1,750 mg/week, and 7% met the DRI for omega-3 PUFAs of 3,500 mg/week. (**Table 5-4**).

Modeling estimates for the intake of fatty acids using the probabilistic Monte Carlo technique provide a relevant preliminary means of characterizing and estimating the proportion of the population who meet established Dietary Reference Intakes for these subgroups. However, comparing this proportion to the results from the blood plasma fatty acid analysis from the biomonitoring study presents a complex issue, as studies have demonstrated that the association between these measures is subject to significant interindividual variability (Donahue et al., 2009). Despite this, there is evidence in the literature that the FFQ provides an accurate estimate for mean fatty acid intake, and would facilitate individuals and groups to be categorized as either meeting or not meeting Dietary Reference Intakes (MacNaughton et al., 2007; Patterson et al., 2012). Within the scope of this analysis, we incorporated results from the plasma fatty acid

profiles collected in the biomonitoring study to determine the Omega-3 Index for participants of the contaminants biomonitoring study in the Dehcho.

The results of blood omega-3 fatty acid profiles for EPA+DHA from the Dehcho are presented in Table 5-7. The groupings outlined in the Omega-3 Index are categorized according to risk of death from coronary heart disease as a function of the relative weight percentage values for EPA+DHA in blood. Overall, respondents from the Dehcho demonstrated a relatively low Omega-3 Index (1.92%; GM 1.81% - **Table 5-7**), falling within the category associated with "very low" cardioprotective benefits from blood levels of EPA+DHA. 91% of participants from the Dehcho fell within the category associated with very low cardioprotective benefit, while 6.7% of participants demonstrated levels associated with low cardioprotective benefit and 2.5% associated with moderate benefit (**Table 5-7**). No respondents demonstrated levels of EPA+DHA associated with high cardioprotective benefit.

5.3.4 Sensitivity analysis

The results of the sensitivity analyses conducted demonstrated that the proportion of the population consuming Northern Pike and Walleye were the largest contributors (22% and 21%, respectively) to the variance for total methylmercury intake and were the most sensitive inputs within the distribution for total mercury exposure, each with correlation coefficients of 0.40 (**Supplementary Table B5**). For fatty acid intake, the intake rate of Lake Whitefish contributed to the most variance for all input variables for all fatty acid subgroups by a significant margin, with correlation coefficients for DHA, EPA+DHA, total omega-3 PUFAs, and total PUFAs of 0.46, 0.49, 0.47, and 0.47, respectively. Following Lake Whitefish, the proportion of the population consuming Lake Trout contributed to a significant proportion of total variance among forecasts for all fatty acid subgroups (**Supplementary Tables B1-B4**).

Table 5-7. Weighted relative percentage of EPA+DHA in total plasma fatty acids (known as the Omega-3 Index) among participants of the Contaminants Biomonitoring Study in the Mackenzie Valley Northwest Territories (n=120).

Blood plasma fatty acid composition	AM (SD)	GM	Percentile					% Participants by category[a]			
			5th	50th	75th	90th	95th	Very Low	Low	Moderate	High
[EPA+DHA] (µg/100 µL)	7.74 (3.10)	7.16	3.53	7.20	9.08	11.8	14.3	-	-	-	-
Omega-3 Index	1.92 (0.72)	1.81	1.04	1.76	2.09	2.78	3.37	91	6.7	2.5	0

[a] The Omega-3 Index, as a function of the relative percentage of EPA+DHA in total blood plasma fatty acids, is subdivided into four categories: [≤2.9 (very low), >2.9–4.0 (low), >4.0–5.2 (moderate), and >5.2 (high)].

Table 5-8. Global Omega-3 Indices for plasma total fatty acids, as compared with results from the five participating Dehcho communities of the contaminants biomonitoring study in the Northwest Territories Mackenzie Valley. The Omega-3 Index represents the relative percentage of EPA+DHA in plasma total fatty acids.

Region	EPA+DHA	Author (Year)[a]	
		Min. Value	Max. Value
Dehcho	1.92	-	
China	3.39 – 3.89	Féart (2008)	Astorg (2009)
Canada	1.54 – 2.42	Metherel (2009)	Metherel (2012)
Spain	2.39 – 4.58	Carrero (2004)	Amiano (2001)
Finland	1.42 – 6.19	Rissanen (2003)	Suominen-Taipal (2010)
United Kingdom	1.71 – 4.03	Rosell (2005)	Sanders (2006)
Japan	3.60 – 12.20	Hirai (2000)	Yamada (2000)
Norway	1.01 – 9.00	Brox (2001)	Grønn (1991)
S. Korea	6.80 – 7.60	Sekikawa (2012)	Nogi (2007)
United States	1.30 – 4.40	Surette (2004)	Motoyama (2009)

[a] Values for the Omega-3 Indices in this table are sourced from studies compiled in Stark et al., (2016b).

Input variables that considered Lake Whitefish (specifically, intake rate, the proportion of consumers among the population, and the concentration of fatty acids in fish tissue) were ranked consistently among the primary contributors to variance and factors of highest sensitivity for all fatty acid subgroups. For all other species, intake rate contributed to at most 5% of variance among fatty acid subgroups, with corresponding correlation coefficients of at most 0.22 (Lake Trout intake for the variance of DHA intake) (**Supplementary Table B1-B4**).

Assumptions within the model corresponding to input variables that characterized the proportion of the population consuming a given fish species dominated in terms of their contribution to variance in MeHg intake, and specifically the proportion predatory fish species consumers. The input variable corresponding to MeHg concentration in Northern Pike, and body weight among the general population, were also among contributors to the variance in MeHg intake (**Supplementary Table B5**).

5.4 Discussion

From the results of the hair mercury analysis, it was observed that participating First Nations peoples of the Dehcho generally fell well within Health Canada's exposure guidelines for mercury, with only a small fraction of the population demonstrating levels that approached or fell slightly above the guideline for hair mercury for the general population.

Based on stable physiological conditions and experimental evidence characterizing methylmercury biokinetics, the toxicokinetics of methylmercury in any given individual can be summarized under steady state ratios that represent the concentration in one biomarker relative to another biomarker. For the purposes of this study, a steady state ratio of 250 μg/g in hair per mg/L in blood was assumed for mercury intake in order to compare the results of this study with

provincial- and national-level biomonitoring studies in both the general population and in other First Nations populations. This ratio is frequently cited in the literature (Bartell et al., 2000; NRC, 2000; Legrand et al., 2010). Using the Hg hair-to-blood conversion ratio of 250, derived for the conversion of hair Hg levels to those in whole blood by the Joint Food and Agriculture Organization of the UN (FAO) and the World Health Organization Expert Committee on Food Additives (WHO, 2004), total Hg exposure from this study of Dehcho participants was compared to results from Cycle 1 of the Canadian Health Measures Survey, the First Nations Biomonitoring Initiative, and results from the First Nations Food, Nutrition, and Environment Studies in British Columbia, Alberta, Manitoba, and Ontario (Health Canada, 2010b; Chan et al., 2011; Chan et al., 2012; AFN, 2013; Chan et al., 2014; Chan et al., 2016). Mercury exposure profiles from the results of the biomonitoring study indicated that hair Hg values among Dehcho participants were similar to converted Hg values from the FNBI, however the mean and geometric mean values from this study were higher than observed in the CHMS (**Table 5-9**). Importantly, however, the FNBI, CHMS, and FNFNES from Manitoba and British Columbia reported exclusively on weighted values, while this study reports raw or unweighted data. Weighted data are adjusted to ensure that all subgroups of the population are not under- or over-represented in the respondent group and that survey findings can be generalized to the survey population. In contrast, unweighted data consider all respondents surveyed, and is representative only of the participants in the study. Furthermore, this study examined respondents aged 6 and above, while the study population in the majority of the biomonitoring surveys in Table 5-9, except for the CHMS, reported results for an adult population. Importantly however, despite demonstrating comparatively higher hair Hg levels than other survey reports, profiles of hair Hg

exposure among the Dehcho population generally fell below Health Canada's guidance value of 6 mg/kg.

Table 5-9. Hair total mercury (in mg/kg) among participants of the Dehcho who consented to hair collection, compared to results from the pilot year of the First Nations Biomonitoring Initiative, results from the 2004 Inuit Health Survey, Cycle I of the Canadian Health Measures Survey, and the First Nations Food, Nutrition and Environment Study.

Study	Age	N	Mean (95% CI)	GM (95% CI)
This Study	6 +	212	0.74 (0.61 – 0.88)	0.38 (0.30 – 0.47)
FNBI[a]	20 +	473	0.62* (0.30 – 0.94)	0.24* (0.13 – 0.44)
IHS[ab]	18 – 74	917	4.32* (4.02 – 4.62)	2.57* (2.41 – 2.75)
CHMS[a]	6 – 79	5319	-	0.17* (0.14 – 0.22)
FNFNES AB	19 +	369	0.19*	0.08* (<LOD – 0.11)
FNFNES ON	19 +	744	0.41*	0.19* (0.16 – 0.23)
FNFNES MB	19 +	236	0.33* (0.09 – 0.57)	0.13* (0.08 – 0.22)
FNFNES BC	19 +	487	0.59* (0.36 – 0.83)	0.36* (0.25 – 0.53)

[a] Values for exposure use the established hair-to-blood conversion factor of 250 proposed by the WHO's JECFA.
[b] Values for exposure reflect a conversion factor of 4.99 nmol/L blood mercury to µg/L blood mercury (WHO, 1995).
[*] Weighted averages are reported, where the data have been adjusted to be generalizable to the target population.

While the Omega-3 Index originally examined EPA+DHA content in RBC membranes, the viability and utility of this method was tested through the use of other biomarkers from similar studies, including EPA+DHA in whole blood (Albert et al., 2002) and plasma phospholipids (Lemaitre et al., 2003). The study suggested a series of target values that outlined the level of cardioprotection conferred through fatty acid intake as a function of the relative percent of EPA+DHA in total fatty acids in the blood. Specifically, values for the relative percent of EPA+DHA in total FAs less than or equal to 4% are among the lowest grouping for what might be considered cardioprotective, and values greater than or equal to 8% were among desirable target values for the Omega-3 Index (Harris and Von Schacky, 2004). Stark et al., (2016) further adapted this approach in an extensive global survey, where studies reporting blood omega-3 PUFA levels of EPA+DHA were systematically identified, and the results of which, based on the geographic region or study population, were assigned into a series of four discrete

ranges corresponding to the relative weighted percentage of EPA+DHA in RBC equivalents. For plasma total fatty acids, equivalent ranges for these EPA+DHA weight percentage values [≤2.9 (very low), >2.9–4.0 (low), >4.0–5.2 (moderate), >5.2 (high)] served to identify countries or regions potentially at an increased risk of chronic disease due in part to EPA+DHA status, and were calculated according to equations described in previous studies (Stark et al., 2016b). Despite Dehcho participants demonstrating a mean Omega-3 Index associated with low cardioprotective benefits, other Canadian studies characterizing this metric among the general population have reported similar findings. Stark et al., (2016) compiled all studies examining fatty acid compositions of plasma lipids in the Canadian general population. Interestingly, and similarly to the findings described herein, studies examining the Canadian general population demonstrated Omega-3 Indices that fell within the lowest category associated with the cardioprotective effects of EPA+DHA (1.54 – 2.42). Regions exhibiting levels associated with high cardioprotective benefit included Japan, South Korea, as well as Denmark, Norway, and regions with Indigenous populations or populations not adapted to Western dietary patterns (**Table 5-8**) (Stark et al., 2016b). Comparatively, levels of EPA+DHA in total fatty acids associated were associated with moderate cardioprotective benefit in a Cree population in Northern Canada. Findings from the blood fatty acid analysis indicate that the Omega-3 Index for the Dehcho population falls in the same category to that of the Canadian general population and of many other populations worldwide, with other Canadian studies demonstrating Omega-3 Indices associated with very low cardioprotective benefit (Stark et al., 2016b). However, the cardioprotective benefits of omega-3 PUFA consumption are of particular significance to First Nations and other Indigenous people of Canada. The burden of cardiovascular disease among Indigenous peoples in Canada has been increasingly recognized in recent decades, with studies

demonstrating age-standardized cardiovascular disease mortality rate to be 30% higher in First Nations men and 76% higher in First Nations women than non-Indigenous cohort members (Tjepkema et al., 2012). As such, promoting the increased dietary intake of traditionally harvested country foods is a significant health priority in First Nations populations, where food insecurity remains a complex a multi-faceted issue (Public Policy Forum, 2015).

Based on the findings from this study and the output from the model, 34% of total weekly fish intake, and 67% of methylmercury intake is attributable to two predatory fish species frequently consumed in the Dehcho, Northern Pike and Walleye (**Table 5-1**). These two species are well documented in previous studies and in this thesis to have elevated mercury concentration profiles, and specifically among lakes of the Dehcho, due primarily to their trophic status as predatory, piscivorous fish species (Evans et al., 2005; Reyes et al., 2016). Comparatively, among those trial values that exceeded the 95th percentile value for weekly MeHg intake, Northern Pike and Walleye contributed in combination to 50% of total weekly fish intake, and 83% of total weekly MeHg intake (**Table 5-3**). In contrast, other piscivorous species, including Burbot and Lake Trout, contributed to only 2% and 8% of total weekly MeHg intake, respectively (**Table 5-**3). This corresponds directly with the results of the sensitivity analysis, where it was determined that the primary drivers of MeHg exposure among the population were the proportion of the population consuming specifically Northern Pike and Walleye. These results support current initiatives underway by the GNWT Department of Health and Social Services aiming to promote the health benefits of fish consumption while advising that limiting the intake of larger predatory fish (e.g., Walleye and Northern Pike), may help to lower people's exposure to mercury.

There are many factors to be considered in the development of dietary advisories that guide public consumption of country foods in order to effectively mitigate any potential health risks associated with contaminant exposure. For remote subarctic communities of the Dehcho, country foods contribute to improved food security and impart significant sociocultural and nutritional benefits that must inherently weigh into the balance of risks and benefits when these dietary notices are communicated. Most importantly, any public health messaging or interventions warning consumers of the risks associated with country food consumption should be easily understood, communicated in a manner that is culturally appropriate and relevant to the sociocultural practices of Dehcho communities, and include specific alternatives that can continue to promote nutritional adequacy while limiting exposure to contaminants.

There are several limitations to consider within the scope of this study, that combined have the potential to introduce a degree of variability and uncertainty in the results from both the human biomonitoring of mercury exposure and fatty acid nutrition within the population of the Dehcho. Notably, despite being a viable, culturally relevant measure for characterizing patterns of dietary country food consumption patterns, the Food Frequency Questionnaire employed to estimate country food intake can be subject to bias in the participant's ability to recall and attempt to characterize their consumption of fish on a weekly basis, based on dietary patterns over the previous year. Furthermore, there is a significant degree of variability in seasonal fish consumption patterns, which might further influence reported intake. However, measures were taken in several communities to account for this variability by surveying participants to estimate and quantify the effects of seasonality on intake.

Moreover, the contaminants biomonitoring study was implemented to characterize the risks and benefits of country food consumption. In this sense, recruitment may be skewed to

underrepresent those who are not frequent consumers of country foods among the population, and participants would arguably be more likely to be consumers of country foods, as community members who are not consumers of country foods may feel the study does not pertain to them. However, the more likely issue is that survey responses pertaining to patterns of country food consumption are biased according to perceptions amongst study respondents about the nature of their diet and what they should be eating. In either event, it is possible that FFQ data illustrate inflated patterns of dietary country food consumption among participants of the Dehcho. This would result in potentially overstated exposure estimates from the output of the dose reconstruction model. Furthermore, instead of using a ratio of 250:1 to compare the results from the hair mercury analysis of this study to national benchmarks (e.g., results of the FNBI and CHMS), a better approach would involve the analysis of blood mercury profiles among participants. The 250 hair-to-blood conversion factor applied to compare results of the biomonitoring study to national studies (e.g., CHMS and FNBI) using hair Hg is a method commonly used in risk and exposure assessment to facilitate the conversion of MeHg hair sample results to circulating MeHg blood levels. This ratio corresponds to the average of values for individuals (140-370) reported in available published studies, which included vulnerable populations (Grandjean et al., 1999; Weihe et al., 2002; WHO, 2004). While this method has been reported to provide an accurate reflection of converted hair-to-blood Hg ratios (Berglund et al., 2005; Johnsson et al., 2005), other studies have noted considerable limitations to the use of this factor as an indicator of either blood or hair Hg levels (Budtz-Jorgensen et al., 2004; Tsuchiya et al., 2012). Notably, on an individual level, quantified hair-to-blood ratios have been demonstrated to exhibit significant variability, and any use of this ratio to establish individual risk may not be an accurate representation of unique physiological and pharmacokinetic

characteristics (Liberda et al., 2014). Applying the 250:1 hair:blood ratio to compare the results of the biomonitoring study with the CHMS and FNBI introduces uncertainty, and future studies examining contaminant profiles in the Dehcho population will benefit from pairing blood Hg measurements as a part of a broader, more exhaustive biomonitoring program. While these data are available from the contaminants biomonitoring study described herein, they were excluded from the scope of this thesis project due to limited sample size. While many participants chose to give samples of hair, fewer blood samples were collected during the biomonitoring study. An analysis of blood mercury and fatty acids will be conducted after subsequent sampling years have provided a more robust profiles for participants of the Dehcho region.

Further, this study presents a preliminary summary of unweighted mercury exposure profiles among respondents of the Dehcho. While possible that reported Hg profiles may be truly representative of community exposure, the findings may be influenced by the demographic distribution of the study population, and weighting the data would permit inferences from participants included in the sample to the Dehcho population as a whole. In future work, controlling for age and sex, as well as by smoking status and body weight, will also facilitate more meaningful comparisons to provincial- and national-level metals biomonitoring studies, .

To model body weight among participants of the contaminants biomonitoring study in the Dehcho, upper and lower truncation bounds at the 5^{th} and 95^{th} percentiles were applied to body weight data in order to closely approximate ranges typically recommended for use in human health risk assessment. In doing so, the truncation of the body weight distribution among Dehcho participants may have precipitated a more constricted distribution around measures of central tendency. Future studies would benefit by pursuing an improved understanding of how truncating body weight distributions can influence the estimation of dose and risk. Body weight

data would facilitate the assessment of risk by modeling exposure profiles among young children, women of childbearing age and pregnant women separately from the general population according to body weight data specific to these demographics, and would increase the utility, accuracy and significance of the model's output.

Probabilistic exposure modeling is a systematic and comprehensive approach to evaluate the risks to human health from drivers of exposure to environmental contaminants, but inherent in these models are sources of both uncertainty and variability that can influence the model's ability to accurately estimate true profiles of exposure. Mercury and fatty acid exposure uncertainty from country food consumption in the Dehcho could arise from an incomplete analysis of common methods of food preparation that shape how these foods are consumed in the region. While details pertaining to food preparation methods were collected during the FFQ, mercury and fatty acid analyses of fish samples were performed exclusively on frozen tissue. Studies have examined the effects of cooking method on the bioaccessibility of mercury and fatty acids within the tissues of fish (Ouédraogo and Amyot, 2011; Costa et al., 2015). A more complete characterization of exposure to fatty acids and mercury from wild-harvested fish species of the Dehcho could include analyses in tissue mercury and fatty acids under a series of different cooking preparation methods. Further, the model's estimates for nutrient and contaminant exposure are based on aggregate data for both country food consumption patterns, and mercury and omega-3 PUFA profiles on a species-basis across the Dehcho. This approach does not account for lake-based differences in mercury and omega-3 PUFA profiles among fish species. To further improve the model's accuracy and relevance, the model design could incorporate lake-specific contaminant and nutrient information, as well as personal or community-specific consumption patterns that outline the lakes from which frequently-

consumed food products are often harvested. The design of the Food Frequency Questionnaire included questions probing these details, and together with lake-specific nutrient and contaminant data would facilitate the inclusion of this element in future modelling efforts. Regional approaches to risk-benefit communication would provide messaging based around results that are more representative on a community-specific basis.

5.5 Conclusion

This study represents the first attempt to model and estimate mercury and fatty exposure profiles among communities of the Dehcho region in the Mackenzie Valley of the Northwest Territories in a comprehensive risk-benefit assessment of dietary country food use. While this study presents the use of mercury and fatty acid profiles to characterize these risks and benefits, this work presents only a subcomponent of what will in the future represent a balanced approach to manage and communicate the risks posed to subarctic First Nations populations from country food consumption. By comparison to the results of the contaminants biomonitoring study, the output from the probabilistic model described herein appear to illustrate an overly conservative estimate of risk to mercury exposure from country foods. As the most likely reason for this, the input parameters included within this model represent only a subset of total exposure to mercury and omega-3 PUFA intake. A Total Diet Assessment would be facilitated through a more complete model that included contaminant and nutrient profiles as well as the dietary consumption patterns for both country foods and market foods. This approach would provide greater insight into a broader range of sources of contaminant exposure and nutrient intake, and would provide more context into the relative contribution of country foods to contaminant exposure through the diet. However, the model's output demonstrated similarities in estimates

for fatty acid profiles of exposure, in that First Nations participants of the Dehcho generally fall within levels that are considered low in terms of benefiting from the cardioprotective effects conferred through fatty acid intake. Future work would benefit from incorporating lake-based differences in mercury and fatty acids, along with consumer preferences in terms of from what lakes these fish are most commonly sourced, in order to more accurately characterize profiles of contaminant exposure.

6. Thesis Conclusions

This thesis project measured mercury and fatty acids in wild-harvested freshwater fish species, explored quantitative methods of risk-benefit analysis and communication, and profiled mercury and fatty acids in participating First Nations people of the Dehcho region in the Mackenzie Valley of the Northwest Territories. The results of this study demonstrate that, in comparison to estimated dietary methylmercury intake from the output of the Monte Carlo-based probabilistic dose reconstruction model, the vast majority of Dehcho participants of the contaminants biomonitoring study are at low risk for exceeding methylmercury dietary guidance values, and generally profiles of exposure fell well within hair mercury guidance values outlined by Health Canada (Health Canada, 2010). Furthermore, participating members of the Dehcho First Nation demonstrated relatively low levels of EPA+DHA as a relative percentage of total blood plasma fatty acids, an indicator of very low cardioprotective effects associated with the consumption of these essential micronutrients.

Future studies in probabilistic dietary risk assessment in First Nations communities of the Dehcho will need to incorporate a component to the model that characterizes risk not only within the general population, but in demographics most vulnerable to the risks associated with mercury exposure, including young children, women of childbearing age, and pregnant women. The majority of regional and federal fish consumption advisories are designed specifically to tailor messaging towards these subpopulations. Future studies that build upon this work with a larger dataset should explore and characterize estimates of exposure in a model unique to pregnant women, women of childbearing age and young children, and use the corresponding guidance values to quantify this risk. An essential component of risk characterization from methylmercury exposure is to quantify risk in potentially susceptible groups where certain subgroups of the

population are particularly vulnerable to its adverse human health effects. The model may be a conservative estimate for exposure within the general population, but in order to effectively characterize risk in vulnerable subgroups, exposure to MeHg should be modeled accordingly. This would include building in relevant body weight data and dietary patterns from FFQ data from these subgroups, and using reference values that correspond to these demographics.

Additionally, incorporating bioavailability factors into the exposure assessment process by modeling country food intake would serve to provide increasingly accurate and realistic estimates of exposure and risk. Standard models of human health risk assessment incorporate an adjustment factor to account for the amount of methylmercury estimated to reach systemic circulation, often assuming conservatively 95% to 100% of ingested MeHg is bioavailable (Bradley et al., 2017). This may result in a certain degree of inaccuracy in estimating MeHg exposure, and would influence the quantitative assessment of risks and benefits associated with country food consumption. As there are currently no established validation methods for mercury bioavailability studies, it would prove difficult to incorporate these elements within the design of a probabilistic model to predict mercury exposure unless this limitation is addressed. Future research focusing on validating these measures through detailed epidemiologic study and further biomarker analyses would facilitate our understanding of Hg bioavailability and assimilation, and may lead to more nuanced assessments of methylmercury risks from the consumption of fish and other country foods (Bradley et al., 2017).

The findings from this study serve to reinforce the importance of wild-harvested fish and other country foods in the diet of subarctic First Nations communities of the Dehcho. Taken in combination, the studies presented in this thesis serve as the first of their kind in the Dehcho region to propose the development of a probabilistic dose reconstruction model where input

parameters that shape the model are defined by contaminant and fatty acid profiles in locally-harvested country foods, and paired with extensive dietary consumption patterns from surveys conducted in participating communities. Made possible through the co-located environmental and human health monitoring supported by the Northern Contaminants Program in the Dehcho region, this research represents a unique opportunity to pair human biomarker data with fish nutrient and contaminant profiles. Pairing these data facilitates future study to more accurately estimate mercury and omega-3 PUFA exposure using consumption habits characterized by patterns of both intake frequency and geographic preferences for the harvesting of country foods.

The results of this study reflect the information provided by respondents of participating First Nations communities of the Dehcho, and serve as an important preliminary component of an extensive multidisciplinary project to characterize the risks and benefits of country food consumption in subarctic indigenous communities. Participants from Dehcho communities have been generally at low risk for exceeding guidance values for mercury exposure. Future work should continue to build on further understanding the perception of risk associated with country food consumption in communities of the Dehcho, and gauging what sources of information are most effective in communicating the risks and benefits of country foods. Broadly, this work will empower subarctic Canadian First Nations peoples to make informed dietary choices that promote the consumption of country foods, and support future of risk-benefit communication strategies and health promotion initiatives that will serve to inform public health messaging around the safe consumption of these Northern dietary staples.

References

Adelson, N. (2005). The embodiment of inequity: health disparities in Aboriginal Canada. Canadian Journal of Public Health / Revue Canadienne de Sante'e Publique *96*, S45-S61.

AFN (2013). First Nations Biomonitoring Initiative - National Results (2011).

Albert, C.M., Campos, H., Stampfer, M.J., Ridker, P.M., Manson, J.E., Willett, W.C., and Ma, J. (2002). Blood levels of long-chain n–3 fatty acids and the risk of sudden death. New England Journal of Medicine *346*, 1113-1118.

Albert, C.M., Oh, K., Whang, W., Manson, J.E., Chae, C.U., Stampfer, M.J., Willett, W.C., and Hu, F.B. (2005). Dietary alpha-linolenic acid intake and risk of sudden cardiac death and coronary heart disease. Circulation *112*, 3232-3238.

Amiano, P., Dorronsoro, M., De Renobales, M., de Gordoa, J.R., and Irigoien, I. (2001). Very-long-chain omega-3 fatty acids as markers for habitual fish intake in a population consuming mainly lean fish: the EPIC cohort of Gipuzkoa. European Journal of Clinical Nutrition, *55*, 827-833.

Amin-Zaki, L., Majeed, M.A., Clarkson, T.W., and Greenwood, M.R. (1978). Methylmercury poisoning In Iraqi children: clinical observations over two years. The British Medical Journal *1*, 613-616.

Anishnabe History. (2017). Survival Mode. Accessed May 20, 2017. Available at: http://www.anishinabe-history.com/reservations/dehcho.shtml.

Angerer, J., Ewers, U., and Wilhelm, M. (2007). Human biomonitoring: state of the art. International journal of hygiene and environmental health *210*, 201-228.

Ariya, P.A., Dastoor, A.P., Amyot, M., Schroeder, W.H., Barrie, L., Anlauf, K., Raofie, F., Ryzhkov, A., Davignon, D., Lalonde, J., *et al.* (2004). The Arctic: a sink for mercury. Tellus B *56*, 397-403.

Ashton, C.W., and Duffie, D. (2011). Chronic kidney disease in Canada's First Nations: results of an effective cross-cultural collaboration. Healthcare Quarterly (Toronto, Ont.) *14*(3), 42.

Astorg, P., Bertrais, S., Laporte, F., Arnault, N., Estaquio, C., Galan, P., ... and Hercberg, S. (2008). Plasma n-6 and n-3 polyunsaturated fatty acids as biomarkers of their dietary intakes: a cross-sectional study within a cohort of middle-aged French men and women. European Journal of Clinical Nutrition, *62*, 1155-1161.

Barbosa, A.C., Silva, S.R.L., and Dorea, J.G.D. (1998). Concentration of mercury in hair of indigenous mothers and infants from the Amazon Basin. Arch Environ Contam Toxicol *334*, 100-105.

Barrie, L.A., Gregor, D., Hargrave, B., Lake, R., Muir, D., Shearer, R., Tracey, B., and Bidleman, T. (1992). Arctic contaminants: sources, occurrence and pathways. Science of The Total Environment *122*, 1-74.

Bartell, S.M., Ponce, R.A., Sanga, R.N., and Faustman, E.M. (2000). Human variability in mercury toxicokinetics and steady state biomarker ratios. Environmental research *84*, 127-132.

Beckford, C.L., Jacobs, C., Williams, N., and Nahdee, R. (2010). Aboriginal environmental wisdom, stewardship, and sustainability: lessons from the Walpole Island First Nations, Ontario, Canada. The Journal of Environmental Education *41*, 239-248.

Beilin, L.J., Mori, T.A., Vandongen, R., Morris, J., Burke, V., and Ritchie, J. (1993). The effects of omega- 3 fatty acids on blood pressure and serum lipids in men at increased risk of cardiovascular disease. Journal of hypertension. Supplement: official journal of the International Society of Hypertension *11*, S318-319.

Bélanger, M.-C., Mirault, M.-E., Dewailly, E., Plante, M., Berthiaume, L., Noël, M., and Julien, P. (2008). Seasonal mercury exposure and oxidant-antioxidant status of James Bay sport fishermen. Metabolism *57*, 630-636.

Bergdahl, I.A., and Skerfving, S. (2008). Biomonitoring of lead exposure—alternatives to blood. Journal of Toxicology and Environmental Health, Part A *71*, 1235-1243.

Berglund, F. (1971). Methylmercury in fish: a toxicologic-epidemiologic evaluation of risks: report from an expert group. Nordisk Hygienisk Tidskrift *4*, 19-364.

Berglund, M., Lind, B., Björnberg, K.A., Palm, B., Einarsson, Ö., and Vahter, M. (2005). Inter-individual variations of human mercury exposure biomarkers: a cross-sectional assessment. Environmental Health *4*, 20.

Berti, P.R., Receveur, O., Chan, H.M., and Kuhnlein, H.V. (1998). Dietary exposure to chemical contaminants from traditional food among adult Dene/Métis in the Western Northwest Territories, Canada. Environmental research *76*, 131-142.

Bisgaard, H., Stokholm, J., Chawes, B.L., Vissing, N.H., Bjarnadóttir, E., Schoos, A.-M.M., Wolsk, H.M., Pedersen, T.M., Vinding, R.K., and Thorsteinsdóttir, S. (2016). Fish oil–derived fatty acids in pregnancy and wheeze and asthma in offspring. New England Journal of Medicine *375*, 2530-2539.

Blanchet, C., Dewailly, E., Ayotte, P., Bruneau, S., Receveur, O., and Holub, B.J. (2000). Contribution of selected traditional and market foods to the diet of Nunavik Inuit women. Canadian Journal of Dietetic Practice and Research *61*, 50.

Bloch, M.H., and Qawasmi, A. (2011). Omega-3 fatty acid supplementation for the treatment of children with Attention-Deficit/Hyperactivity Disorder symptomatology: systematic review and meta-analysis. Journal of the American Academy of Child & Adolescent Psychiatry *50*, 991-1000.

Bloom, N.S. (1992). On the chemical form of mercury in edible fish and marine invertebrate tissue. Canadian Journal of Fisheries and Aquatic Sciences *49*, 1010-1017.

Bogen, K.T., Cullen, A.C., Frey, H.C., and Price, P.S. (2009). Probabilistic exposure analysis for chemical risk characterization. *Toxicological Sciences 109*, 4-17.

Branco, V., Canário, J., Lu, J., Holmgren, A., and Carvalho, C. (2012). Mercury and selenium interaction in vivo: effects on thioredoxin reductase and glutathione peroxidase. Free Radical Biology and Medicine *52*, 781-793.

Brox, J., Olaussen, K., Østerud, B., Elvevoll, E.O., Bjørnstad, E., Brenn, T., ... and Iversen, H. (2001). A long-term seal-and cod-liver-oil supplementation in hypercholesterolemic subjects. Lipids, *36*, 7-13.

Budtz-Jørgensen, E., Grandjean, P., Jørgensen, P.J., Weihe, P., and Keiding, N. (2004). Association between mercury concentrations in blood and hair in methylmercury-exposed subjects at different ages. An Ecosystem Approach to Health Effects of Mercury in the St Lawrence Great Lakes *95*, 385-393.

Budtz-Jørgensen, E., Grandjean, P., Keiding, N., White, R.F., and Weihe, P. (2000). Benchmark dose calculations of methylmercury-associated neurobehavioural deficits. Toxicology letters *112–113*, 193-199.

Budtz-Jørgensen, E., Jørgensen, P.J., Weihe, P., and Grandjean, P. (2005). Umbilical cord mercury concentration as biomarker of prenatal exposure to methylmercury. Environmental health perspectives *113*, 905-908.

Burmaster, D.E., and von Stackelberg, K. (1991). Using Monte Carlo simulations in public health risk assessments: estimating and presenting full distributions of risk. Journal of exposure analysis and environmental epidemiology *1*, 491-512.

Byczkowski, J.Z., Preedy, V.R., and Watson, R.R. (2005). Methylmercury toxicity: Pharmacokinetics and toxicodynamic aspects. Reviews in Food and Nutrition Toxicity *3*, 61-84.

Calon, F., and Cole, G. (2007). Neuroprotective action of omega-3 polyunsaturated fatty acids against neurodegenerative diseases: evidence from animal studies. Prostaglandins, Leukotrienes and Essential Fatty Acids *77*, 287-293.

Canada's Public Policy Forum. (2015). Toward food security in Canada's North: summary report.

Cardoso, C., Bandarra, N., Lourenço, H., Afonso, C., and Nunes, M. (2010). Methylmercury risks and EPA+DHA benefits associated with seafood consumption in Europe. Risk analysis *30*, 827-840.

Carrero, J.J., Baró, L., Fonollá, J., González-Santiago, M., Martínez-Férez, A., Castillo, R., ... and López-Huertas, E. (2004). Cardiovascular effects of milk enriched with ω-3

polyunsaturated fatty acids, oleic acid, folic acid, and vitamins E and B6 in volunteers with mild hyperlipidemia. Nutrition, *20*, 521-527.

Carta, P., Flore, C., Alinovi, R., Ibba, A., Tocco, M.G., Aru, G., Carta, R., Girei, E., Mutti, A., Lucchini, R., *et al.* (2003). Sub-clinical neurobehavioral abnormalities associated with low level of mercury exposure through fish consumption. Neurotoxicology *24*, 617-623.

Cernichiari, E., Brewer, R., Myers, G.J., Marsh, D.O., Lapham, L.W., Cox, C., Shamlaye, C.F., Berlin, M., Davidson, P.W., and Clarkson, T.W. (1995). Monitoring methylmercury during pregnancy: maternal hair predicts fetal brain exposure. . Neurotoxicology *16*, 705-710.

Chan, H.M., Trifonopoulos, M., Ing, A., Receveur, O., and Johnson, E. (1999). Consumption of freshwater fish in Kahnawake: risks and benefits. Environmental research *80*, S213-S222.

Chan, L., Receveur, O., Batal, M., David, W., Schwartz, H., Ing, A., Fediuk, K., Black, A., and Tikhonov, C. (2014). First Nations Food, Nutrition and Environment Study (FNFNES): Results from Ontario (2011/2012). Ottawa: University of Ottawa.

Chan, L., Receveur, O., Batal, M., David, W., Schwartz, H., Ing, A., Fediuk, K., and Tikhonov, C. (2016). First Nations Food, Nutrition and Environment Study (FNFNES): Results from Alberta 2013. Ottawa, ON: University of Ottawa.

Chan, L., Receveur, O., Sharp, D., Schwartz, H., and Tikhonov, C. (2012). First Nations Food, Nutrition and Environment Study (FNFNES): Results from Manitoba (2010) (University of Northern British Columbia).

Chan, L., Receveur, O., Sharp, D., Schwartz, H., Tikhonov, C., and Mimeault, C. (2011). First nations food, nutrition and environment study (fnfnes): results from British Columbia (2008/2009) (University of Northern British Columbia).

Choi, A.L., Weihe, P., Budtz-Jørgensen, E., Jørgensen, P.J., Salonen, J.T., Tuomainen, T.P., Murata, K., Nielsen, H.P., Petersen, M.S., Askham, J., *et al.* (2009). Methylmercury exposure and adverse cardiovascular effects in Faroese whaling men. Environmental health perspectives *117*, 367-372.

Choy, C.A., Popp, B.N., Kaneko, J.J., and Drazen, J.C. (2009). The influence of depth on mercury levels in pelagic fishes and their prey. Proceedings of the National Academy of Sciences *106*, 13865-13869.

Clarkson, T.W. (2002). The three modern faces of mercury. Environmental health perspectives *110*, 11-23.

Clarkson, T.W., Magos, L., and Myers, G.J. (2003). The toxicology of mercury – current exposures and clinical manifestations. N Engl J Med *349*, 1731-1737.

Clarkson, T.W., Vyas, J.B., and Ballatori, N. (2007). Mechanisms of mercury disposition in the body. American Journal of Industrial Medicine *50*, 757-764.

Clewell III, H.J. (1995). The application of physiologically based pharmacokinetic modeling in human health risk assessment of hazardous substances. Decision Subtances Methodologies for Human Health Risk Assessment of Toxic Substances *79*, 207-217.

Cohen, J.T., Bellinger, D.C., Connor, W.E., Kris-Etherton, P.M., Lawrence, R.S., Savitz, D.A., Shaywitz, B.A., Teutsch, S.M., and Gray, G.M. (2005). A quantitative risk – benefit analysis of changes in population fish consumption. American Journal of Preventive Medicine *29*, 325-334.e326.

Colombo, J., Kannass, K.N., Shaddy, D.J., Kundurthi, S., Maikranz, J.M., Anderson, C.J., Blaga, O.M., and Carlson, S.E. (2004). Maternal DHA and the development of attention in infancy and toddlerhood. Child development *75*, 1254-1267.

Compeau, G.C., and Bartha, R. (1985). Sulfate-reducing bacteria: principal methylators of mercury in anoxic estuarine sediment. Applied and Environmental Microbiology *50*, 498-502.

Conquer, J., Tierney, M., Zecevic, J., Bettger, W., and Fisher, R. (2000). Fatty acid analysis of blood plasma of patients with alzheimer's disease, other types of dementia, and cognitive impairment. Lipids *35*, 1305-1312.

Costa, S., Afonso, C., Cardoso, C., Batista, I., Chaveiro, N., Nunes, M.L., and Bandarra, N.M. (2015). Fatty acids, mercury, and methylmercury bioaccessibility in salmon (Salmo salar) using an in vitro model: Effect of culinary treatment, pp. 268-276.

Davis, J.A., Gift, J.S., and Zhao, Q.J. (2011). Introduction to benchmark dose methods and U.S. EPA's benchmark dose software (BMDS) version 2.1.1. TRAC 2008/2009 meeting *254*, 181-191.

Debes, F., Budtz-Jørgensen, E., Weihe, P., White, R.F., and Grandjean, P. (2006). Impact of prenatal methylmercury exposure on neurobehavioral function at age 14 years. Neurotoxicology and teratology *28*, 536-547.

Dewailly, É., Blanchet, C., Gingras, S., Lemieux, S., and Holub, B. (2003). Fish consumption and blood lipids in three ethnic groups of Québec (canada). Lipids *38*, 359-365.

Dewailly, E., Blanchet, C., Gingras, S., Lemieux, S., and Holub, B.J. (2002). Cardiovascular disease risk factors and n-3 fatty acid status in the adult population of James Bay Cree. The American Journal of Clinical Nutrition *76*, 85-92.

Dewailly, E., Blanchet, C., Lemieux, S., Sauvé, L., Gingras, S., Ayotte, P., and Holub, B.J. (2001). N-3 fatty acids and cardiovascular disease risk factors among the Inuit of Nunavik. The American Journal of Clinical Nutrition *74*, 464-473.

DHSS (2016). Site-Specific Fish Consumption Advice (Northwest Territories Department of Social Services Webpage). Accessed March 28, 2017. Available at: http://www.hss.gov.nt.ca/en/services/fish-consumption-guidance/site-specific-fish-consumption-advice.

Díez, S. (2009). Human health effects of methylmercury exposure. Reviews of Environmental Contaminants and Toxicology 111-132.

Dolbec, J., Mergler, D., Larribe, F., Roulet, M., Lebel, J., and Lucotte, M. (2001). Sequential analysis of hair mercury levels in relation to fish diet of an Amazonian population, Brazil. Science of The Total Environment *271*, 87-97.

Dolbec, J., Mergler, D., Sousa Passos, C.J., Sousa de Morais, S., and Lebel, J. (2000). Methylmercury exposure affects motor performance of a riverine population of the Tapajós river, Brazilian Amazon. International Archives of Occupational and Environmental Health *73*, 195-203.

Domingo, J.L. (2016). Nutrients and chemical pollutants in fish and shellfish. Balancing health benefits and risks of regular fish consumption. Critical Reviews in Food Science and Nutrition *56*, 979-988.

Donahue, S.M.A., Rifas-Shiman, S.L., Olsen, S.F., Gold, D.R., Gillman, M.W., & Oken, E. (2009). Associations of maternal prenatal dietary intake of n-3 and n-6 fatty acids with maternal and umbilical cord blood levels. Prostaglandins, Leukotrienes and Essential Fatty Acids *80*, 289-296.

Donaldson, S.G., Van Oostdam, J., Tikhonov, C., Feeley, M., Armstrong, B., Ayotte, P., Boucher, O., Bowers, W., Chan, L., Dallaire, F., *et al.* (2010). Environmental contaminants and human health in the Canadian Arctic. Science of The Total Environment *408*, 5165-5234.

Driedger, S., Cooper, E., Jardine, C., Furgal, C., and Bartlett, J. (2013). Communicating Risk to Aboriginal Peoples: First Nations and Metis Responses to H1N1 Risk Messages. e71106. PLoS ONE *8*.

Driscoll, C.T., Mason, R.P., Chan, H.M., Jacob, D.J., and Pirrone, N. (2013). Mercury as a global pollutant: sources, pathways, and effects. Environmental Science and Technology *47*, 4967-4983.

Dunstan, J.A., Simmer, K., Dixon, G., and Prescott, S.L. (2008). Cognitive assessment of children at age 2(1/2) years after maternal fish oil supplementation in pregnancy: a randomised controlled trial. Archives of disease in childhoodFetal and neonatal edition *93*, F45-50.

Dyck, R., Osgood, N., Lin, T.H., Gao, A., and Stang, M.R. (2010). Epidemiology of diabetes mellitus among First Nations and non-First Nations adults. Canadian Medical Association Journal *182*, 249-256.

Dziechciarz, P., Horvath, A., and Szajewska, H. (2010). Effects of n-3 long-chain polyunsaturated fatty acid supplementation during pregnancy and/or lactation on neurodevelopment and visual function in children: a systematic review of randomized controlled trials. Journal of the American College of Nutrition *29*, 443-454.

Dong, Z., Liu, Y., Duan, L., Bekele, D., and Naidu, R. (2015). Uncertainties in human health risk assessment of environmental contaminants: A review and perspective. Environment International *85* 120-132.

EFSA (2010). Scientific opinion on dietary reference values for fats, including saturated fatty acids, polyunsaturated fatty acids, monounsatureated fatty acids, trans fatty acids, and cholesterol. EFSA Journal *8*, 1461-1566.

Egeland, G.M., Johnson-Down, L., Cao, Z.R., Sheikh, N., and Weiler, H. (2011). Food insecurity and nutrition transition combine to affect nutrient intakes in Canadian arctic communities. The Journal of nutrition *141*, 1746-1753.

Elahi, M.M., Kong, Y.X., and Matata, B.M. (2009). Oxidative stress as a mediator of cardiovascular disease. Oxidative Medicine and Cellular Longevity *2*, 259-269.

Eslick, G.D., Howe, P.R.C., Smith, C., Priest, R., and Bensoussan, A. (2009). Benefits of fish oil supplementation in hyperlipidemia: a systematic review and meta-analysis. International Journal of Cardiology *136*, 4-16.

Esteban, M., and Castaño, A. (2009). Non-invasive matrices in human biomonitoring: a review. Environment International *35*, 438-449.

Evans, M.S., Lockhart, W.L., Doetzel, L., Low, G., Muir, D., Kidd, K., Stephens, G., and Delaronde, J. (2005). Elevated mercury concentrations in fish in lakes in the Mackenzie River Basin: the role of physical, chemical, and biological factors. Science of the Total Environment *351*, 479-500.

FAO (2010). fatty acids in human nutrition. Report of an expert consultation. FAO Food and Nutrition Paper *91*, 1-166.

Farina, M., Rocha, J.B.T., and Aschner, M. (2011). Mechanisms of methylmercury-induced neurotoxicity: Evidence from experimental studies. International Symposium on Cell Signaling *89*, 555-563.

Féart, C., Peuchant, E., Letenneur, L., Samieri, C., Montagnier, D., Fourrier-Reglat, A., and Barberger-Gateau, P. (2008). Plasma eicosapentaenoic acid is inversely associated with severity of depressive symptomatology in the elderly: data from the Bordeaux sample of the Three-City Study. The American Journal of Clinical Nutrition, *87*, 1156-1162.

Fediuk, K., Hidiroglou, N., Madère, R., and Kuhnlein, H.V. (2002). Vitamin C in Inuit Traditional Food and Women's Diets. Journal of Food Composition and Analysis *15*, 221-235.

Feng, X., Li, P., Qiu, G., Wang, S., Li, G., Shang, L., Meng, B., Jiang, H., Bai, W., Li, Z., *et al.* (2008). Human exposure to methylmercury through rice intake in mercury mining areas, Guizhou province, China. Environmental Science and Technology *42*, 326-332.

Ferreira-Sae, M.-C.S., Gallani, M.-C.B.J., Nadruz, W., Rodrigues, R.C.M., Franchini, K.G., Cabral, P.C., and Sales, M.L. (2009). Reliability and validity of a semi-quantitative FFQ for sodium intake in low-income and low-literacy Brazilian hypertensive subjects. Public health nutrition *12*, 2168-2173.

Fieldhouse, P., and Thompson, S. (2012). Tackling food security issues in indigenous communities in Canada: The Manitoba experience. Nutrition & Dietetics *69*, 217-221.

Folch, J., Lees, M., and Sloane Stanley, G.H. (1957). A simple method for the isolation and purification of total lipides from animal tissues. The Journal of biological chemistry *226*, 497-509.

Forsyth, D.S., Casey, V., Dabeka, R.W., and McKenzie, A. (2004). Methylmercury levels in predatory fish species marketed in Canada. Food additives and contaminants *21*, 849-856.

Friendship, K.A., and Furgal, C.M. (2012). The role of Indigenous knowledge in environmental health risk management in Yukon, Canada. International journal of circumpolar health *71*.

Furgal, C., Powell, S., and Myers, H. (2005). Digesting the Message About Contaminants and Country Foods in the Canadian North: A Review and Recommendations for Future Research and Action. Arctic *58*, 103-103.

Gagné, D., Blanchet, R., Lauzière, J., Vaissière, É., Vézina, C., Ayotte, P., Déry, S., and O'Brien, H.T. (2012). Traditional food consumption is associated with higher nutrient intakes in Inuit children attending childcare centres in Nunavik. International journal of circumpolar health *71*.

Garland, M., Morris, J.S., Rosner, B.A., Stampfer, M.J., Spate, V.L., Baskett, C.J., Willett, W.C., and Hunter, D.J. (1993). Toenail trace element levels as biomarkers: reproducibility over a 6-year period. Cancer Epidemiology and Prevention Biomarkers 2, 493-497.

Gaziano, J.M., Hennekens, C.H., O'Donnell, C.J., Breslow, J.L., and Buring, J.E. (1997). Fasting Triglycerides, High-Density Lipoprotein, and Risk of Myocardial Infarction. Circulation *96*, 2520-2525.

Gauba, P., Shakeel, M., & Gaur, S. (2014). Mercury Neurotoxicity: a review of case studies. Asian Journal of Multidisciplinary Studies *3*.

Geleijnse, J.M., Giltay, E.J., Grobbee, D.E., Donders, A.R.T., and Kok, F.J. (2002). Blood pressure response to fish oil supplementation: metaregression analysis of randomized trials. Journal of hypertension *20*, 1493.

Ginsberg, G.L., and Toal, B.F. (2009). Quantitative approach for incorporating methylmercury risks and omega-3 fatty acid benefits in developing species-specific fish consumption advice. Environmental health perspectives *117*, 267.

Gochfeld, M. (2003). Cases of mercury exposure, bioavailability, and absorption. Special Issue on Methodologies for Assessing Exposures to Metals: Speciation, Bioaccessibility and Bioavailability in the Environment, Food and Feed *56*, 174-179.

Graham, J.D., and Wiener, J.B. (1997). Risk versus risk tradeoffs in protecting health and the environment, 1st Harvard University Press pbk. ed. edn (Cambridge, Mass.: Harvard University Press).

Grandjean, P., Budtz-Jorgensen, E., White, R.F., Jorgensen, P.J., Weihe, P., Debes, F., and Keiding, N. (1999). Methylmercury exposure biomarkers as indicators of neurotoxicity in children aged 7 years. American Journal of Epidemiology *150*, 301-305.

Grandjean, P., Murata, K., Budtz-Jørgensen, E., and Weihe, P. (2004). Cardiac autonomic activity in methylmercury neurotoxicity: 14-year follow-up of a Faroese birth cohort. The Journal of pediatrics *144*, 169-176.

Grandjean, P., Weihe, P., White, R.F., Debes, F., Araki, S., Yokoyama, K., Murata, K., SØRensen, N., Dahl, R., and JØRgensen, P.J. (1997). Cognitive Deficit in 7-Year-Old Children with Prenatal Exposure to Methylmercury. Neurotoxicology and teratology *19*, 417-428.

Grønn, M., Gørbitz, C., Christensen, E., Levorsen, A., Ose, L., Hagve, T.A., and Christophersen, B.O. (1991). Dietary n-6 fatty acids inhibit the incorporation of dietary n-3 fatty acids in thrombocyte and serum phospholipids in humans: a controlled dietetic study. Scandinavian Journal of Clinical and Laboratory Investigation, *51*, 255-263.

Grotto, D., de Castro, M.M., Barcelos, G.R.M., Garcia, S.C., and Barbosa Jr, F. (2009). Low level and sub-chronic exposure to methylmercury induces hypertension in rats: nitric oxide depletion and oxidative damage as possible mechanisms. Archives of Toxicology *83*, 653-662.

Guallar, E., Sanz-Gallardo, M., Veer, P.v.t., Bode, P., Aro, A., Gómez-Aracena, J., Kark, J.D., Riemersma, R.A., Martín-Moreno, J.M., and Kok, F.J. (2002). Mercury, Fish Oils, and the Risk of Myocardial Infarction. N Engl J Med *347*, 1747-1754.

Hanning, R.M., Royall, D., Toews, J.E., Blashill, L., Wegener, J., and Driezen, P. (2009). Web-based food behaviour questionnaire: validation with grades six to eight students. Canadian Journal of Dietetic Practice and Research *70*, 172-178.

Hansen, J.C., & Gilman, A.P. (2005). Exposure of Arctic populations to methylmercury from consumption of marine food: an updated risk-benefit assessment. International Journal of Circumpolar Health *64*, 121-136.

Harada, M. (1995). Minamata disease: methylmercury poisoning in Japan caused by environmental pollution, M. Harada, ed., pp. 1-24.

Harris, W.S., Mozaffarian, D., Lefevre, M., Toner, C.D., Colombo, J., Cunnane, S.C., Holden, J.M., Klurfeld, D.M., Morris, M.C., and Whelan, J. (2009). Towards establishing dietary

reference intakes for eicosapentaenoic and docosahexaenoic acids. The Journal of nutrition *139*, 804S-819S.

Harris, W.S., and Von Schacky, C. (2004). The Omega-3 Index: a new risk factor for death from coronary heart disease? Preventive medicine *39*, 212-220.

Health Canada (2007). Human health risk assessment of mercury in fish and health benefits of fish consumption. Ottawa, Ontario: Bureau of Chemical Safety.

Health Canada (2010a). Guidance on Human Health Preliminary Quantitative Risk Assessment (PQRA), Version 2.0. Part I.

Health Canada (2010b). Report on Human Biomonitoring of Environmental Chemicals in Canada: Results of the Canadian Health Measures Survey Cycle 1 (2007-2009) (Health Canada).

Health Canada (2011). Eating well with Canada's food guide (Queen's Printer Ottawa).

Hellberg, R.S., DeWitt, C.A.M., and Morrissey, M.T. (2012). Risk-benefit analysis of seafood consumption: A review. Comprehensive reviews in food science and food safety *11*, 490-517.

Hirai, K., Horiuchi, R., Ohno, Y., Higuchi, H., and Asano, Y. (2000). Lower eicosapentaenoic acid and higher arachidonic acid levels in Sera of young adults in the Netherlands than in Japan. Environmental Health and Preventive Medicine, *5*, 60-65.

Hodson, L., Skeaff, C.M., and Fielding, B.A. (2008). Fatty acid composition of adipose tissue and blood in humans and its use as a biomarker of dietary intake. Progress in lipid research *47*, 348-380.

Hooijmans, C. R., Pasker-de Jong, P., de Vries, R., & Ritskes-Hoitinga, M. (2012). The effects of long-term omega-3 fatty acid supplementation on cognition and Alzheimer's pathology in animal models of Alzheimer's disease: a systematic review and meta-analysis. *Journal of Alzheimer's Disease*, *28*(1), 191-209.

Horrocks, L.A., and Yeo, Y.K. (1999). Health benefits of docosahexaenoic acid (DHA). Pharmacological Research *40*, 211-225.

Horvat, M., Nolde, N.a., Fajon, V., Jereb, V., Logar, M., Lojen, S., Jacimovic, R., Falnoga, I., Liya, Q., Faganeli, J., *et al.* (2003). Total mercury, methylmercury and selenium in mercury polluted areas in the province Guizhou, China. Pathways and processes of mercury in the environment Selected papers presented at the sixth International Conference on Mercury as Global Pollutant, Minamata, Japan, Oct 15-19, 2001 *304*, 231-256.

Hultman, P., and Nielsen, J.B. (2001). The effect of dose, gender, and non-H-2 genes in murine mercury-induced autoimmunity. Journal of Autoimmunity *17*, 27-37.

ISSFAL (2004). Recommendations for intakes of polyunsaturated fatty acids in healthy adults. ISSFAL Newsl *11*, 12-25.

Jacobs, D.R., Mebane, I.L., Bangdiwala, S.I., Criqui, M.H., Tyroler, H.A., and For The Lipid Research Clinics, P. (1990). High Density Lipoprotein cholesterol as a predictor of cardiovascular disease mortality in men and women: the follow-up study of the Lipid Research Clinics prevalence study. American Journal of Epidemiology *131*, 32-47.

Jamieson, J.A., Weiler, H.A., Kuhnlein, H.V., and Egeland, G.M. (2012). Traditional food intake is correlated with iron stores in Canadian Inuit men. The Journal of nutrition *142*, 764-770.

JECFA. (1972). Evaluation of mercury, lead, cadmium and the food additives amaranth, diethylpyrocarbonate, and octyl gallate. World Health, 1.

Johnsson, C., Schütz, A., and Sällsten, G. (2005). Impact of consumption of freshwater fish on mercury levels in hair, blood, urine, and alveolar air. Journal of Toxicology and Environmental Health, Part A *68*, 129-140.

Karagas, M.R., Choi, A.L., Oken, E., Horvat, M., Schoeny, R., Kamai, E., Cowell, W.J., Grandjean, P., and Korrick, S.A. (2012). Evidence on the Human Health Effects of Low Level Methylmercury Exposure. Environmental health perspectives.

Kavlock, R.J., Daston, G.P., Deroas, C., Fenner-Crisp, P., Gray, L.E.K.S., Lucier, G., Luster, M., Mac, M.J., Maczka, C., Miller, R., *et al.* (1996). Research needs for the risk assessment of health and environmental effects of endocrine disruptors: a report of the U.S. EPA-sponsored workshop. Environmental health perspectives *104 Suppl 4*, 715.

Kerin, E.J., Gilmour, C.C., Roden, E., Suzuki, M.T., Coates, J.D., and Mason, R.P. (2006). Mercury methylation by dissimilatory iron-reducing bacteria. Applied and Environmental Microbiology *72*, 7919-7921.

Khan, M.A., and Wang, F. (2009). Mercury-selenium compounds and their toxicological significance: Toward a molecular understanding of the mercury-selenium antagonism. Environmental Toxicology and Chemistry *28*, 1567-1577.

Kim, Y. N., Kim, Y. A., Yang, A. R., & Lee, B. H. (2014). Relationship between blood mercury level and risk of cardiovascular diseases: results from the Fourth Korea National Health and Nutrition Examination Survey (KNHANES IV) 2008–2009. Preventive Nutrition and Food Science *19*, 333.

King, J.K., Kostka, J.E., Frischer, M.E., and Saunders, F.M. (2000). Sulfate- Reducing Bacteria Methylate Mercury at Variable Rates in Pure Culture and in Marine Sediments. Applied and Environmental Microbiology *66*, 2430.

Kitson, A.P., Patterson, A.C., Izadi, H., and Stark, K.D. (2009). Pan-frying salmon in an eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) enriched margarine prevents EPA and DHA loss. Food Chemistry *114*, 927-932.

Kjeldsen-Kragh, J., Lund, J.A., Riise, T., Finnanger, B., Haaland, K., Finstad, R., Mikkelsen, K., and Forre, O. (1992). Dietary omega-3 fatty acid supplementation and naproxen treatment in patients with rheumatoid arthritis. The Journal of rheumatology *19*, 1531-1536.

Kjellström, T., Kennedy, P., Wallis, S., Stewart, A., Friberg, L., Lind, B., Wutherspoon, T., and Mantell, C. (1989). Physical and mental development of children with prenatal exposure to mercury from fish. Stage 2. Interviews and psychological tests at age 6.

Knobeloch, L., Tomasallo, C., and Anderson, H. (2011). Biomonitoring as an intervention against methylmercury exposure. Public health reports (Washington, DC: 1974) *126*, 568-574.

Koletzko, B., Lien, E., Agostoni, C., Böhles, H., Campoy, C., Cetin, I., Decsi, T., Dudenhausen, J.W., Dupont, C., and Forsyth, S. (2008). The roles of long-chain polyunsaturated fatty acids in pregnancy, lactation and infancy: review of current knowledge and consensus recommendations. Journal of perinatal medicine *36*, 5-14.

Kremer, J., Michalek, A., Lininger, L., Huyck, C., Bigauoette, J., Timchalk, M., Rynes, R., Zieminski, J., and Bartholomew, L. (1985). Effects of manipulation of dietary fatty acids on clinical manifestations of rheumatoid arthritis. The Lancet *325*, 184-187.

Kris-Etherton, P.M., Grieger, J.A., and Etherton, T.D. (2009). Dietary reference intakes for DHA and EPA. Prostaglandins, Leukotrienes and Essential Fatty Acids *81*, 99-104.

Kris-Etherton, P.M., Innis, S., and Ammerican, D.A. (2007). Position of the American Dietetic Association and Dietitians of Canada: dietary fatty acids. Journal of the American Dietetic Association *107*, 1599-1611.

Kuhnlein, H., Erasmus, B., Creed-Kanashiro, H., Englberger, L., Okeke, C., Turner, N., Allen, L., and Bhattacharjee, L. (2006). Indigenous peoples' food systems for health: finding interventions that work. Public Health Nutrition *9*, 1013-1019.

Kuhnlein, H., and Receveur, O. (2007). Local Cultural Animal Food Contributes High Levels of Nutrients for Arctic Canadian Indigenous Adults and Children1,2. The Journal of nutrition *137*, 1110-1114.

Kuhnlein, H.V., and Chan, H.M. (2000). Environment and contaminants in traditional food systems of Northern Indigenous peoples, pp. 595-626.

Kuhnlein, H.V., and Receveur, O. (1996). Dietary Change and Traditional Food Systems of Indigenous Peoples. Annual Review of Nutrition *16*, 417-442.

Kuhnlein, H.V., Receveur, O., Soueida, R., and Egeland, G.M. (2004). Arctic indigenous peoples experience the nutrition transition with changing dietary patterns and obesity. The Journal of nutrition *134*, 1447.

Labonté, M.È., Cyr, A., Baril-Gravel, L., Royer, M.M., and Lamarche, B. (2012). Validity and reproducibility of a web-based, self-administered food frequency questionnaire. European journal of clinical nutrition *66*, 166-173.

Laird, B.D., Goncharov, A.B., Egeland, G.M., and Chan, H.M. (2013). Dietary Advice on Inuit Traditional Food Use Needs to Balance Benefits and Risks of Mercury, Selenium, and n3 Fatty Acids. Journal of Nutrition *143*, 923-930.

Laird, B.D., Shade, C., Gantner, N., Chan, H.M., and Siciliano, S.D. (2009). Bioaccessibility of mercury from traditional northern country foods measured using an in vitro gastrointestinal model is independent of mercury concentration. Science of the Total Environment *407*, 6003-6008.

Lam, H.S., Kwok, K.M., Chan, P.H.Y., So, H.K., Li, A.M., Ng, P.C., and Fok, T.F. (2013). Long term neurocognitive impact of low dose prenatal methylmercury exposure in Hong Kong. Environment International *54*, 59-64.

Lau, C.S., Morley, K.D., and Belch, J.J. (1993). Effects of fish oil supplementation on non-steroidal anti-inflammatory drug requirement in patients with mild rheumatoid arthritis--a double-blind placebo controlled study. British journal of rheumatology *32*, 982-989.

Lebel, J., Mergler, D., Branches, F., Lucotte, M., Amorim, M., Larribe, F., and Dolbec, J. (1998). Neurotoxic Effects of Low-Level Methylmercury Contamination in the Amazonian Basin. Environmental research *79*, 20-32.

Legrand, M., Feeley, M., Tikhonov, C., Schoen, D., and Li - Muller, A. (2010). Methylmercury blood guidance values for Canada. (Commentary)(Report). Canadian Journal of Public Health *101*, 28.

Lemaitre, R.N., King, I.B., Mozaffarian, D., Kuller, L.H., Tracy, R.P., and Siscovick, D.S. (2003). n− 3 Polyunsaturated fatty acids, fatal ischemic heart disease, and nonfatal myocardial infarction in older adults: the Cardiovascular Health Study. The American journal of clinical nutrition *77*, 319-325.

Lemire, M., Kwan, M., Laouan-Sidi, A.E., Muckle, G., Pirkle, C., Ayotte, P., and Dewailly, E. (2015). Local country food sources of methylmercury, selenium and omega-3 fatty acids in Nunavik, Northern Quebec. Special Issue: Mercury in Canada's North *509–510*, 248-259.

Lemming, E.W., Nälsén, C., Becker, W., Ridefelt, P., Mattisson, I., and Lindroos, A.K. (2015). Relative validation of the dietary intake of fatty acids among adults in the Swedish National Dietary Survey using plasma phospholipid fatty acid composition. Journal of nutritional science *4*.

Liberda, E.N., Tsuji, L.J., Martin, I.D., Ayotte, P., Dewailly, E., and Nieboer, E. (2014). The complexity of hair/blood mercury concentration ratios and its implications. Environmental research *134*, 286-294.

Lin, S., Herdt-Losavio, M., Chen, M., Luo, M., Tang, J., and Hwang, S.-A. (2014). Fish consumption patterns, knowledge and potential exposure to mercury by race. International journal of environmental health research *24*, 291-303.

Lin, T.-H., Huang, Y.-L., and Huang, S.-F. (1996). Lipid peroxidation in liver of rats administrated with methyl mercuric chloride. Biological trace element research *54*, 33-41.

Lindberg, A., Ask Björnberg, K., Vahter, M., and Berglund, M. (2004). Exposure to methylmercury in non-fish-eating people in Sweden. Environmental research *96*, 28-33.

Lockhart, W.L., Stern, G.A., Low, G., Hendzel, M., Boila, G., Roach, P., Evans, M.S., Billeck, B.N., DeLaronde, J., and Friesen, S. (2005). A history of total mercury in edible muscle of fish from lakes in northern Canada. Science of the Total Environment *351*, 427-463.

Lockhart, W.L., Wagemann, R., Tracey, B., Sutherland, D., and Thomas, D.J. (1992). Presence and implications of chemical contaminants in the freshwaters of the Canadian Arctic. Science of The Total Environment *122*, 165-243.

Macintosh, D.L., Williams, P.L., Hunter, D.J., Sampson, L.A., Morris, S.C., Willett, W.C., and Rimm, E.B. (1997). Evaluation of a food frequency questionnaire- food composition approach for estimating dietary intake of inorganic arsenic and methylmercury. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology *6*, 1043.

Mahaffey, K.R. (2004). Fish and shellfish as dietary sources of methylmercury and the n-3 fatty acids, eicosahexaenoic acid and docosahexaenoic acid: risks and benefits. An Ecosystem Approach to Health Effects of Mercury in the St Lawrence Great Lakes *95*, 414-428.

Mahaffey, K.R., Clickner, R.P., and Bodurow, C.C. (2004). Blood organic mercury and dietary mercury intake: National Health and Nutrition Examination Survey, 1999 and 2000. Environmental health perspectives *112*, 562-570.

Mahaffey, K.R., Sunderland, E.M., Chan, H.M., Choi, A.L., Grandjean, P., Marien, K., Oken, E., Sakamoto, M., Schoeny, R., Weihe, P., *et al.* (2011). Balancing the benefits of n-3 polyunsaturated fatty acids and the risks of methylmercury exposure from fish consumption. Nutrition reviews *69*, 493-508.

Malcolm, C., McCulloch, D.L., Montgomery, C., Shepherd, A., and Weaver, L. (2003). Maternal docosahexaenoic acid supplementation during pregnancy and visual evoked potential development in term infants: a double blind, prospective, randomised trial. Archives of Disease in Childhood *88*, F383-F390.

Malm, O. (1998). Gold Mining as a Source of Mercury Exposure in the Brazilian Amazon. Environmental research *77*, 73-78.

Marks, K.A., Kitson, A.P., and Stark, K.D. (2013). Hepatic and plasma sex differences in saturated and monounsaturated fatty acids are associated with differences in expression of

elongase 6, but not stearoyl-CoA desaturase in Sprague–Dawley rats. Genes & nutrition *8*, 317-327.

Maycock, B.J., and Benford, D.J. (2007). Risk assessment of dietary exposure to methylmercury in fish in the UK, pp. 185-190.

McAuley, C., and Knopper, L.D. (2011). Impacts of traditional food consumption advisories: Compliance, changes in diet and loss of confidence in traditional foods. Environmental Health *10*, 55-55.

McDowell, M.A., Dillon, C.F., Osterloh, J., Bolger, P.M., Pellizzari, E., Fernando, R., Montes de Oca, R., Schober, S.E., Sinks, T., Jones, R.L., and Mahaffey, K.R. (2004). Hair mercury levels in US children and women of childbearing age: reference range data from NHANES 1999–2000. Environmental Health Perspectives *112*, 1165.

McNaughton, S.A., Hughes, M.C., & Marks, G.C. (2007). Validation of a FFQ to estimate the intake of PUFA using plasma phospholipid fatty acids and weighed foods records. British Journal of Nutrition *97*, 561-568.

Mergler, D., Anderson, H.A., Chan, L.H.M., Mahaffey, K.R., Murray, M., Sakamoto, M., and Stern, A.H. (2007). Methylmercury exposure and health effects in humans: a worldwide concern, A.H. Stern, ed., pp. 3-11.

Metcalf, S.W., and Orloff, K.G. (2004). Biomarkers of exposure in community settings. Journal of Toxicology and Environmental Health, Part A *67*, 715-726.

Metherel, A.H., Armstrong, J.M., Patterson, A.C., and Stark, K.D. (2009). Assessment of blood measures of n-3 polyunsaturated fatty acids with acute fish oil supplementation and washout in men and women. Prostaglandins, Leukotrienes and Essential Fatty Acids, *81*, 23-29.

Metherel, A.H., Buzikievich, L.M., Charkhzarin, P., Patterson, A.C., Peel, A.C., Howorth, A.M., ... and Stark, K.D. (2012). Omega-3 polyunsaturated fatty acid profiling using fingertip-prick whole blood does not require overnight fasting before blood collection. Nutrition Research, *32*, 547-556.

Morrissette, J., Takser, L., St-Amour, G., Smargiassi, A., Lafond, J., and Mergler, D. (2004). Temporal variation of blood and hair mercury levels in pregnancy in relation to fish consumption history in a population living along the St. Lawrence River. An Ecosystem Approach to Health Effects of Mercury in the St Lawrence Great Lakes *95*, 363-374.

Morton, J., Mason, H., Ritchie, K., and White, M. (2004). Comparison of hair, nails and urine for biological monitoring of low level inorganic mercury exposure in dental workers. Biomarkers *9*, 47-55.

Motoyama, K. R., Curb, J. D., Kadowaki, T., El-Saed, A., Abbott, R. D., Okamura, T., ... and Kadota, A. (2009). Association of serum n− 6 and n− 3 polyunsaturated fatty acids with

lipids in 3 populations of middle-aged men. The American Journal of Clinical Nutrition, *90*, 49-55.

Mozaffarian, D. (2009). Fish, mercury, selenium and cardiovascular risk: current evidence and unanswered questions, D. Mozaffarian, ed., pp. 1894-1916.

Mozaffarian, D., Geelen, A., Brouwer, I.A., Geleijnse, J.M., Zock, P.L., and Katan, M.B. (2005). Effect of Fish Oil on Heart Rate in Humans: A Meta-Analysis of Randomized Controlled Trials. Circulation *112*, 1945-1952.

Mozaffarian, D., and Rimm, E.B. (2006). Fish intake, contaminants, and human health: evaluating the risks and the benefits. Jama *296*, 1885-1899.

Mozaffarian, D., Shi, P., Morris, J.S., Spiegelman, D., Grandjean, P., Siscovick, D.S., Willett, W.C., and Rimm, E.B. (2011). Mercury exposure and risk of cardiovascular disease in two US cohorts. New England Journal of Medicine *364*, 1116-1125.

Muir, D., Braune, B., DeMarch, B., Norstrom, R., Wagemann, R., Lockhart, L., Hargrave, B., Bright, D., Addison, R., Payne, J., *et al.* (1999). Spatial and temporal trends and effects of contaminants in the Canadian Arctic marine ecosystem: a review. Science of The Total Environment *230*, 83-144.

Myers, G.J., Davidson, P.W., Cox, C., Shamlaye, C.F., Palumbo, D., Cernichiari, E., Sloane-Reeves, J., Wilding, G.E., Kost, J., and Huang, L.-S. (2003). Prenatal methylmercury exposure from ocean fish consumption in the Seychelles child development study. The lancet *361*, 1686-1692.

Neff, M.R., Bhavsar, S.P., Braekevelt, E., and Arts, M.T. (2014). Effects of different cooking methods on fatty acid profiles in four freshwater fishes from the Laurentian Great Lakes region. Food Chemistry *164*, 544-550.

Neuringer, M., Anderson, G.J., and Connor, W.E. (1988). The essentiality of n-3 fatty acids for the development and function of the retina and brain. Annual review of nutrition *8*, 517-541.

Nielsen, N.H., Storm, H.H., Gaudette, L.A., and Lanier, A.P. (1996). Cancer in Circumpolar Inuit 1969-1988. Acta Oncologica *35*, 621-628.

Nogi, A., Yang, J., Li, L., Yamasaki, M., Watanabe, M., Hashimoto, M., and Shiwaku, K. (2007). Plasma n-3 polyunsaturated fatty acid and cardiovascular disease risk factors in Japanese, Korean and Mongolian workers. Journal of Occupational Health, *49*, 205-216.

NRC (2000). Toxicological effects of methylmercury. National Research Council (Washington, DC: National Academy Press).

Oken, E., and Bellinger, D.C. (2008). Fish consumption, methylmercury and child neurodevelopment. Current opinion in pediatrics *20*, 178-183.

Oken, E., Kleinman, K.P., Berland, W.E., Simon, S.R., Rich-Edwards, J.W., and Gillman, M.W. (2003). Decline in fish consumption among pregnant women after a national mercury advisory. Obstetrics & Gynecology *102*, 346-351.

Olsen, S.F., Østerdal, M.L., Salvig, J.D., Mortensen, L.M., Rytter, D., Secher, N.J., and Henriksen, T.B. (2008). Fish oil intake compared with olive oil intake in late pregnancy and asthma in the offspring: 16 y of registry-based follow-up from a randomized controlled trial. The American journal of clinical nutrition *88*, 167-175.

Ouédraogo, O., and Amyot, M. (2011). Effects of various cooking methods and food components on bioaccessibility of mercury from fish. Environmental research *111*, 1064-1069.

Pakseresht, M., and Sharma, S. (2010). Validation of a quantitative food frequency questionnaire for Inuit population in Nunavut, Canada. Journal of human nutrition and dietetics *23*, 67-74.

Palmisano, F., Cardellicchio, N., and Zambonin, P.G. (1995). Speciation of mercury in dolphin liver: a two-stage mechanism for the demethylation accumulation process and role of selenium. Marine environmental research *40*, 109-121.

Park, J.-D., and Zheng, W. (2012). Human exposure and health effects of inorganic and elemental mercury. Journal of Preventive Medicine and Public Health *45*, 344-352.

Patterson, A.C., Hogg, R.C., Kishi, D.M., & Stark, K.D. (2012). Biomarker and dietary validation of a Canadian food frequency questionnaire to measure eicosapentaenoic and docosahexaenoic acid intakes from whole food, functional food, and nutraceutical sources. Journal of the Academy of Nutrition and Dietetics *112*, 1005-1014.

Paulsson, K., and Lundbergh, K. (1989). The selenium method for treatment of lakes for elevated levels of mercury in fish. Science of the Total Environment *87*, 495-507.

Paustenbach, D. (2000). The practice of exposure assessment: A state-of-the- art review (Reprinted from Principles and Methods of Toxicology, 4th edition, 2001). Journal Of Toxicology And Environmental Health-Part B-Critical Reviews *3*, 179-291.

Ralston, N.V.C., and Raymond, L.J. (2010). Dietary selenium's protective effects against methylmercury toxicity. Toxicology *278*, 112-123.

Ratelle, M., Laird, M., Majowicz, S., and Laird, B. (2017). Design and Implementation of Human Biomonitoring in the Northwest Territories Mackenzie Valley under the Northern Contaminants Program (NCP). Health and Place (Submitted).

Receveur, O., Boulay, M., Mills, C., Carpenter, W., and Kuhnlein, H.V. (1996). Variance in food use in Dene/Métis communities. Centre for Indigenous Peoples' Nutrition and Environment (CINE), McGill University, Montreal *198*.

Receveur, O., Kassi, N., Chan, H.M., Berti, P.R., & Kuhnlein, H.V. (1998). Yukon First Nations' assessment of dietary benefit/risk. *Quebec: Centre for Indigenous Peoples' Nutrition and Environment, McGill University*.

Rees, J.R., Sturup, S., Chen, C., Folt, C., and Karagas, M.R. (2007). Toenail mercury and dietary fish consumption. Journal of Exposure Science and Environmental Epidemiology *17*, 25.

Renwick, A.G., Barlow, S.M., Hertz-Picciotto, I., Boobis, A.R., Dybing, E., Edler, L., Eisenbrand, G., Greig, J.B., Kleiner, J., Lambe, J., *et al.* (2003). Risk characterisation of chemicals in food and diet. Risk Characterisation of Chemicals in Food and Diet Final part of Food Safety in Europe (FOSIE): Risk Assessment of Chemicals in Food and Diet *41*, 1211-1271.

Reyes, E.S., Aristizabal Henao, J.J., Kornobis, K.M., Hanning, R.M., Majowicz, S.E., Liber, K., Stark, K.D., Low, G., Swanson, H.K., and Laird, B.D. (2016). Associations between omega-3 fatty acids, selenium content, and mercury levels in wild-harvested fish from the Dehcho Region, Northwest Territories, Canada. Journal of Toxicology and Environmental Health, Part A, 1-14.

Rice, G., Swartout, J., Mahaffey, K., and Schoeny, R. (2000). Derivation of U.S. EPA's oral Reference Dose (RfD) for methylmercury, R. Schoeny, ed., pp. 41-54.

Rice, K.M., Walker Jr, E.M., Wu, M., Gillette, C., and Blough, E.R. (2014). Environmental mercury and its toxic effects. Journal of Preventive Medicine and Public Health *47*, 74.

Richmond, C.A.M., and Ross, N.A. (2009). The determinants of First Nation and Inuit health: A critical population health approach. Health & place *15*, 403-411.

Rissanen, H., Knekt, P., Jarvinen, R., Salminen, I., and Hakulinen, T. (2003). Serum fatty acids and breast cancer incidence. Nutrition and Cancer, *45*, 168-175.

Roman, H.A., Walsh, T.L., Coull, B.A., Dewailly, É., Guallar, E., Hattis, D., Mariën, K., Schwartz, J., Stern, A.H., and Virtanen, J.K. (2011). Evaluation of the cardiovascular effects of methylmercury exposures: current evidence supports development of a dose-response function for regulatory benefits analysis. Environmental health perspectives *119*, 607.

Rosell, M.S., Lloyd-Wright, Z., Appleby, P.N., Sanders, T.A., Allen, N.E., and Key, T.J. (2005). Long-chain n–3 polyunsaturated fatty acids in plasma in British meat-eating, vegetarian, and vegan men. The American Journal of Clinical Nutrition, *82*, 327-334.

Rowland, I.R. (1988). Interactions of the Gut Microflora and the Host in Toxicology. Toxicologic pathology *16*, 147-153.

Ruxton, C. (2011). The benefits of fish consumption. Nutrition Bulletin *36*, 6-19.

Ruxton, C., Reed, S.C., Simpson, M., and Millington, K. (2004). The health benefits of omega-3 polyunsaturated fatty acids: a review of the evidence. Journal of Human Nutrition and Dietetics *17*, 449-459.

Sager, P.R., and Matheson, D.W. (1988). Mechanisms of neurotoxicity related to selective disruption of microtubules and intermediate filaments. Toxicology *49*, 479-492.

Salonen, J.T., Seppänen, K., Lakka, T.A., Salonen, R., and Kaplan, G.A. (2000). Mercury accumulation and accelerated progression of carotid atherosclerosis: a population-based prospective 4-year follow-up study in men in eastern Finland. Atherosclerosis *148*, 265-273.

Sanders, T.A., Gleason, K., Griffin, B., and Miller, G.J. (2006). Influence of an algal triacylglycerol containing docosahexaenoic acid (22: 6n-3) and docosapentaenoic acid (22: 5n-6) on cardiovascular risk factors in healthy men and women. British Journal of Nutrition, *95*, 525-531.

Schuster, R.C., Gamberg, M., Dickson, C., and Chan, H.M. (2011). Assessing risk of mercury exposure and nutritional benefits of consumption of caribou (Rangifer tarandus) in the Vuntut Gwitchin First Nation community of Old Crow, Yukon, Canada. Environmental research *111*, 881-887.

Seabert, T.A., Pal, S., Pinet, B.M., Haman, F., Robidoux, M.A., Imbeault, P., Kruemmel, E.M., Kimpe, L.E., and Blais, J.M. (2014). Elevated Contaminants Contrasted with Potential Benefits of omega-3 Fatty Acids in Wild Food Consumers of Two Remote First Nations Communities in Northern Ontario, Canada. Plos One *9*, e90351-e90351.

Sekikawa, A., Curb, J. D., Ueshima, H., El-Saed, A., Kadowaki, T., Abbott, R. D., ... and Nakamura, Y. (2008). Marine-derived n-3 fatty acids and atherosclerosis in Japanese, Japanese-American, and white men: a cross-sectional study. Journal of the American College of Cardiology, *52*, 417-424.

Seppänen, K., Kantola, M., Laatikainen, R., Nyyssönen, K., Valkonen, V.-P., Kaarlöpp, V., and Salonen, J. (2000). Effect of supplementation with organic selenium on mercury status as measured by mercury in pubic hair. Journal of trace elements in medicine and biology *14*, 84-87.

Setzer, R.W., and Kimmel, C.A. (2003). Use of NOAEL, benchmark dose, and other models for human risk assessment of hormonally active substances. Pure and applied chemistry *75*, 2151-2158.

Sherman, L.S., Blum, J.D., Franzblau, A., and Basu, N. (2013). New insight into biomarkers of human mercury exposure using naturally occurring mercury stable isotopes. Environmental Science & Technology *47*, 3403.

Shimshack, J. P., and Ward, M. B. (2010). Mercury advisories and household health trade-offs. Journal of Health Economics *29*, 674-685.

Stark, K., and Salem, N. (2005). Fast gas chromatography for the identification of fatty acid methyl esters from mammalian samples. Lipid Technology *17*, 181.

Stark, K.D., Henao, J.J.A., Metherel, A.H., and Pilote, L. (2016a). Translating plasma and whole blood fatty acid compositional data into the sum of eicosapentaenoic and docosahexaenoic acid in erythrocytes. Prostaglandins, Leukotrienes and Essential Fatty Acids (PLEFA) *104*, 1-10.

Stark, K.D., Van Elswyk, M.E., Higgins, M.R., Weatherford, C.A., and Salem, N. (2016b). Global survey of the omega-3 fatty acids, docosahexaenoic acid and eicosapentaenoic acid in the blood stream of healthy adults. Progress in lipid research *63*, 132-152.

Steffen, A., Lehnherr, I., Cole, A., Ariya, P., Dastoor, A., Durnford, D., Kirk, J., and Pilote, M. (2015). Atmospheric mercury in the Canadian Arctic. Part I: A review of recent field measurements. Science of the Total Environment *509*, 3-15.

Suominen-Taipale, A.L., Partonen, T., Turunen, A.W., Männistö, S., Jula, A., and Verkasalo, P.K. (2010). Fish consumption and omega-3 polyunsaturated fatty acids in relation to depressive episodes: a cross-sectional analysis. PLoS One, *5*, e10530.

Surette, M. E., Edens, M., Chilton, F. H., and Tramposch, K. M. (2004). Dietary echium oil increases plasma and neutrophil long-chain (n-3) fatty acids and lowers serum triacylglycerols in hypertriglyceridemic humans. The Journal of Nutrition, *134*, 1406-1411.

Swanson, D., Block, R., and Mousa, S.A. (2012). Omega-3 Fatty Acids EPA and DHA: Health Benefits Throughout Life. Advances in Nutrition: An International Review Journal *3*, 1-7.

Swanson, H.K. (2014). Pers Comm.

Swanson, H.K., and Kidd, K.A. (2010). Mercury concentrations in Arctic food fishes reflect the presence of anadromous Arctic charr (Salvelinus alpinus), species, and life history. Environmental science & technology *44*, 3286-3292.

Tian, W., Egeland, G.M., Sobol, I., and Chan, H.M. (2011). Mercury hair concentrations and dietary exposure among Inuit preschool children in Nunavut, Canada. Environment international *37*, 42-48.

Tjepkema, M., Wilkins, R., Goedhuis, N., and Pennock, J. (2012). Cardiovascular disease mortality among First Nations people in Canada, 1991-2001. Chronic diseases and injuries in Canada *32*.

Touyz, R.M., and Briones, A.M. (2011). Reactive oxygen species and vascular biology: implications in human hypertension. Hypertension Research *34*, 5-14.

Tsuchiya, A., Duff, R., Stern, A.H., White, J.W., Krogstad, F., Burbacher, T.M., Faustman, E.M., and Mariën, K. (2012). Single blood-Hg samples can result in exposure misclassification: temporal monitoring within the Japanese community (United States). Environmental Health *11*, 37.

Tsuchiya, A., Hardy, J., Burbacher, T.M., Faustman, E.M., and Marien, K. (2008). Fish intake guidelines: incorporating n-3 fatty acid intake and contaminant exposure in the Korean and Japanese communities. The American Journal of Clinical Nutrition *87*, 1867-1875.

Tulleken, J.E., Limburg, P.C., Muskiet, F.A.J., and Rijswijk, M.H.V. (1990). Vitamin E status during dietary fish oil supplementation in rheumatoid arthritis. Arthritis & Rheumatism *33*, 1416-1419.

Uauy, R., Hoffman, D.R., Mena, P., Llanos, A., and Birch, E.E. (2003). Term infant studies of DHA and ARA supplementation on neurodevelopment: results of randomized controlled trials. The Journal of pediatrics *143*, 17-25.

USEPA (2000). Method 7473, Mercury in solids and solutions by thermal decomposition, amalgamation, and atomic absorption spectrophotometry. Test Methods for Evaluating Solid Waste, Physical/Chemical Methods.

USEPA (2015). Conducting a human health risk assessment.

Valera, B., Muckle, G., Poirier, P., Jacobson, S.W., Jacobson, J.L., & Dewailly, E. (2012). Cardiac autonomic activity and blood pressure among Inuit children exposed to mercury. Neurotoxicology *33*, 1067-1074.

van der Voet, H., de Mul, A., and van Klaveren, J.D. (2007). A probabilistic model for simultaneous exposure to multiple compounds from food and its use for risk–benefit assessment. Food and Chemical Toxicology *45*, 1496-1506.

Van Oostdam, J., Donaldson, S.G., Feeley, M., Arnold, D., Ayotte, P., Bondy, G., Chan, L., Dewaily, E., Furgal, C.M., Kuhnlein, H., *et al.* (2005). Human health implications of environmental contaminants in Arctic Canada: A review. Science of the Total Environment *351*, 165-246.

Van Wijngaarden, E., Beck, C., Shamlaye, C.F., Cernichiari, E., Davidson, P.W., Myers, G.J., and Clarkson, T.W. (2006). Benchmark concentrations for methyl mercury obtained from the 9-year follow-up of the Seychelles Child Development Study. Neurotoxicology *27*, 702-709.

Vázquez, M., Vélez, D., and Devesa, V. (2014). In vitro characterization of the intestinal absorption of methylmercury using a Caco-2 cell model. Chemical research in toxicology *27*, 254-264.

Virtanen, J.K., Voutilainen, S., Rissanen, T.H., Mursu, J., Tuomainen, T.P., Korhonen, M.J., Valkonen, V.P., Seppanen, K., Laukkanen, J.A., and Salonen, J.T. (2005). Mercury, fish oils, and risk of acute coronary events and cardiovascular disease, coronary heart disease, and all-cause mortality in men in eastern Finland. Arteriosclerosis, Thrombosis, and Vascular Biology *25*, 228-233.

von Schacky, C. (2014). Omega-3 index and cardiovascular health. Nutrients *6*, 799-814.

Weihe, P., Hansen, J.C., Murata, K., Debes, F., Jørgensen, P.J., Steuerwald, U., White, R.F., and Grandjean, P. (2002). Neurobehavioral performance of Inuit children with increased prenatal exposure to methylmercury. International Journal of Circumpolar Health *61*, 41-49.

Weiser, M.J., Wynalda, K., Salem, N., Jr., and Butt, C.M. (2015). Dietary DHA during development affects depression-like behaviors and biomarkers that emerge after puberty in adolescent rats. Journal of lipid research *56*, 151-166.

Wiener, J.G., Krabbenhoft, D.P., Heinz, G.H., and Scheuhammer, A.M. (2003). Ecotoxicology of mercury. Handbook of Ecotoxicology *2*, 409-463.

Whanger, P.D. (1992). Selenium in the treatment of heavy metal poisoning and chemical carcinogenesis. Journal of trace elements and electrolytes in health and disease *6*, 209-221.

WHO (1995). Basic Analytical Toxicology, Annex 2: Conversion factors for mass and molar concentrations.

WHO (2004). Evaluation of certain food additives and contaminants: sixty-first report of the joint FAO/WHO expert committee on food additives, Vol 61 (World Health Organization).

Williams, M.C.W., Murphy, E.W., McCarty, H.B., Snyder, B.D., Schrank, C.S., McCann, P.J., and Crimmins, B.S. (2017). Variation in the essential fatty acids EPA and DHA in fillets of fish from the Great Lakes region. Journal of Great Lakes Research.

Yamada, T., Strong, J.P., Ishii, T., Ueno, T., Koyama, M., Wagayama, H., ... and Guzman, M.A. (2000). Atherosclerosis and ω-3 fatty acids in the populations of a fishing village and a farming village in Japan. Atherosclerosis, *153*, 469-481.

Yoneda, S., and Suzuki, K.T. (1997). Equimolar Hg-Se complex binds to selenoprotein P. Biochemical and biophysical research communications *231*, 7-11.

Ysart, G., Miller, P., Croasdale, M., Crews, H., Robb, P., Baxter, M., De L'Argy, C., and Harrison, N. (2000). 1997 UK Total Diet Study-- dietary exposures to aluminium, arsenic, cadmium, chromium, copper, lead, mercury, nickel, selenium, tin and zinc. Food additives and contaminants *17*, 775.

Zhang, H., Chai, Z., and Sun, H. (2007). Human hair as a potential biomonitor for assessing persistent organic pollutants. Environment international *33*, 685-693.

Appendix A: Supplementary Tables and Figures

Supplementary Table A1. Total mercury in wild-harvested freshwater fish caught in the Dehcho region, Northwest Territories, Canada (2013, 2014, 2015).

Fish Species	Lake	N=333	Mercury (µg/g)	
			Range	Mean ± SD
Burbot	Mustard Lake	5	0.090 - 0.134	0.112 ± 0.019
	Trout Lake	9	0.228 - 0.551	0.317 ± 0.101
	Total	**14**	**0.090 - 0.551**	**0.244 ± 0.130**
Cisco	Ekali Lake	5	0.067 - 0.194	0.116 ± 0.061
	Gargan Lake	1	0.080	0.080
	Kakisa Lake	8	0.037 - 0.048	0.043 ± 0.004
	Sanguez Lake	1	0.127	0.127
	Trout Lake	6	0.034 - 0.041	0.038 ± 0.003
	Total	**21**	**0.034 - 0.194**	**0.064 ± 0.045**
Lake Trout	Mustard Lake	39	0.079 - 0.511	0.187 ± 0.081
	Trout Lake	12	0.209 - 0.643	0.341 ± 0.155
	Total	**51**	**0.079 - 0.643**	**0.223 ± 0.121**
Lake Whitefish	Ekali Lake	11	0.056 - 0.128	0.084 ± 0.025
	Gargan Lake	16	0.050 - 0.250	0.128 ± 0.059
	Kakisa Lake	10	0.021 - 0.083	0.044 ± 0.023
	McGill Lake	9	0.090 - 0.320	0.168 ± 0.077
	Sanguez Lake	3	0.088 - 0.150	0.129 ± 0.036
	Tathlina Lake	9	0.040 - 0.130	0.083 ± 0.027
	Trout Lake	10	0.025 - 0.057	0.037 ± 0.009
	Total	**68**	**0.021 - 0.320**	**0.095 ± 0.061**
Northern Pike	Ekali Lake	17	0.129 - 1.100	0.433 ± 0.286
	Gargan Lake	15	0.160 - 1.240	0.412 ± 0.319
	Kakisa Lake	10	0.036 - 0.906	0.295 ± 0.266
	McGill Lake	8	0.120 - 1.430	0.485 ± 0.422
	Mustard Lake	5	0.081 - 0.260	0.156 ± 0.071
	Sanguez Lake	10	0.295 - 3.121	1.343 ± 0.824
	Tathlina Lake	10	0.100 - 0.990	0.374 ± 0.313
	Trout Lake	10	0.073 - 0.286	0.153 ± 0.085
	Total	**85**	**0.036 - 3.121**	**0.469 ± 0.503**
Walleye	Ekali Lake	17	0.097 - 0.457	0.278 ± 0.099
	Kakisa Lake	8	0.109 - 0.667	0.282 ± 0.198
	McGill Lake	7	0.510 - 1.160	0.877 ± 0.246
	Sanguez Lake	7	0.402 - 1.428	0.724 ± 0.355

	Tathlina Lake	9	0.320 - 0.990	0.623 ± 0.240
	Trout Lake	11	0.036 - 0.848	0.293 ± 0.310
	Total	**59**	**0.036 - 1.428**	**0.458 ± 0.323**
Sucker[1]	Kakisa Lake	14	0.02 - 0.16	0.09 ± 0.04
	McGill Lake	8	0.12 - 0.37	0.21 ± 0.1
	Mustard Lake	1	0.15	0.15
	Tathlina Lake	6	0.11 - 0.29	0.21 ± 0.06
	Trout Lake	6	0.09 - 0.13	0.1 ± 0.01
	Total	**35**	**0.02 - 0.37**	**0.140 ± 0.08**
Longnose Sucker	Kakisa Lake	7	0.022 - 0.156	0.080 ± 0.043
	McGill Lake	4	0.120 - 0.370	0.253 ± 0.126
	Mustard Lake	1	0.147	0.147
	Tathlina Lake	1	0.190	0.190
	Trout Lake	6	0.086 - 0.127	0.100 ± 0.015
	Total	**19**	**0.022 - 0.370**	**0.132 ± 0.090**
White Sucker	Kakisa Lake	7	0.037 - 0.147	0.105 ± 0.037
	McGill Lake	4	0.130 - 0.190	0.165 ± 0.025
	Tathlina Lake	5	0.110 - 0.290	0.216 ± 0.067
	Total	**16**	**0.037 - 0.290**	**0.155 ± 0.066**

[1] Combining Longnose and White Sucker data sets.

Supplementary Table A2a. Species- and lake-specific fatty acid profiles for EPA+DHA, EPA+DHA+DPA, total omega-3s, and total PUFAs, of fish harvested in the Dehcho region, Northwest Territories, Canada (N=333).

Fish Species	Lake	N	EPA+DHA (mg/100g)		EPA+DHA+DPA (mg/100g)		Omega-3s (mg/100g)		PUFAs (mg/100g)	
			Range	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD
Burbot	Mustard	5	98 - 128	109 ± 13	109 - 143	123 ± 15	115 - 149	129 ± 16	207 - 255	226 ± 22
	Trout	9	57 - 110	86 ± 16	62 - 119	93 ± 18	68 - 126	100 ± 18	109 - 185	150 ± 24
	Total	**14**	**57 - 128**	**94 ± 19**	**62 - 143**	**104 ± 22**	**68 - 149**	**111 ± 22**	**109 - 255**	**177 ± 44**
Cisco	Ekali	5	145 - 279	192 ± 51	158 - 311	211 ± 58	187 - 500	294 ± 126	252 - 683	400 ± 177
	Gargan	1	316	316	344	344	459	459	621	621
	Kakisa	8	166 - 380	242 ± 64	182 - 439	269 ± 77	213 - 693	352 ± 148	271 - 935	460 ± 205
	Sanguez	1	215	215	238	238	368	368	491	491
	Trout	6	205 - 344	252 ± 60	225 - 383	277 ± 68	296 - 541	375 ± 104	371 - 691	472 ± 134
	Total	**21**	**145 - 380**	**235 ± 61**	**158 - 439**	**259 ± 71**	**187 - 693**	**351 ± 123**	**252 - 935**	**458 ± 167**
Lake Trout	Mustard	39	174 - 606	278 ± 91	186 - 738	328 ± 123	193 - 994	394 ± 199	267 - 1522	561 ± 313
	Trout	12	165 - 2332	898 ± 694	191 - 2813	1080 ± 833	215 - 4247	1530 ± 1267	311 - 5570	2069 ± 1626
	Total	**51**	**165 - 2332**	**424 ± 428**	**186 - 2813**	**505 ± 517**	**193 - 4247**	**662 ± 788**	**267 - 5570**	**916 ± 1036**
Lake Whitefish	Ekali	11	187 - 544	279 ± 102	200 - 612	308 ± 119	223 - 887	393 ± 193	297 - 1354	569 ± 309
	Gargan	16	195 - 378	278 ± 52	214 - 418	308 ± 59	236 - 517	366 ± 85	327 - 816	535 ± 141
	Kakisa	10	205 - 476	321 ± 89	223 - 553	360 ± 106	269 - 774	468 ± 174	355 - 1095	654 ± 265
	McGill	9	187 - 368	240 ± 56	207 - 407	268 ± 62	228 - 471	311 ± 80	304 - 653	454 ± 134
	Sanguez	3	262 - 1048	628 ± 395	288 - 1223	711 ± 474	333 - 2050	1093 ± 875	459 - 3145	1595 ± 1390
	Tathlina	9	225 - 316	268 ± 30	240 - 342	293 ± 33	255 - 408	352 ± 48	349 - 566	493 ± 75
	Trout	10	182 - 349	240 ± 49	195 - 398	263 ± 61	212 - 555	315 ± 112	281 - 859	428 ± 186
	Total	**68**	**182 - 1048**	**288 ± 122**	**195 - 1223**	**320 ± 142**	**212 - 2050**	**401 ± 248**	**281 - 3145**	**573 ± 384**
Northern Pike	Ekali	17	120 - 592	176 ± 109	125 - 643	189 ± 118	135 - 696	204 ± 128	184 - 944	278 ± 173
	Gargan	15	100 - 477	175 ± 86	108 - 515	191 ± 93	115 - 538	200 ± 97	182 - 722	279 ± 126
	Kakisa	10	138 - 215	187 ± 23	150 - 255	210 ± 29	159 - 291	229 ± 38	223 - 387	304 ± 51
	McGill	8	117 - 219	174 ± 38	127 - 246	190 ± 44	136 - 284	209 ± 53	180 - 367	276 ± 66
	Mustard	5	196 - 237	217 ± 17	214 - 257	236 ± 18	224 - 270	247 ± 18	308 - 423	361 ± 43
	Sanguez	10	113 - 707	192 ± 182	120 - 758	205 ± 195	131 - 835	227 ± 215	176 - 1094	305 ± 279
	Tathlina	10	104 - 198	145 ± 26	112 - 222	158 ± 31	117 - 267	169 ± 41	166 - 419	239 ± 71
	Trout	10	166 - 293	205 ± 40	180 - 325	223 ± 47	200 - 432	256 ± 75	250 - 565	329 ± 103
	Total	**85**	**100 - 707**	**181 ± 88**	**108 - 758**	**197 ± 96**	**115 - 835**	**214 ± 107**	**166 - 1094**	**291 ± 142**
Walleye	Ekali	17	132 - 807	231 ± 182	138 - 856	248 ± 196	150 - 909	273 ± 215	200 - 1197	371 ± 287
	Kakisa	8	150 - 192	169 ± 17	168 - 215	189 ± 18	179 - 229	202 ± 20	236 - 312	275 ± 25
	McGill	7	132 - 223	160 ± 30	149 - 248	176 ± 34	161 - 308	195 ± 51	221 - 420	269 ± 68
	Sanguez	7	87 - 613	206 ± 181	96 - 651	221 ± 191	112 - 695	240 ± 202	162 - 916	323 ± 263

	Tathlina	9	121 - 225	162 ± 31	132 - 253	178 ± 36	140 - 285	192 ± 43	209 - 449	284 ± 70
	Trout	11	124 - 238	196 ± 32	135 - 254	210 ± 34	148 - 273	228 ± 36	200 - 357	290 ± 43
	Total	**59**	**87 - 807**	**194 ± 117**	**96 - 856**	**211 ± 126**	**112 - 909**	**229 ± 137**	**162 - 1197**	**312 ± 182**
Sucker[1]	Kakisa	14	175 - 340	245 ± 46	195 - 394	278 ± 55	221 - 510	333 ± 84	297 - 767	474 ± 136
	McGill	8	148 - 291	198 ± 47	164 - 325	221 ± 54	170 - 364	236 ± 66	253 - 505	340 ± 87
	Mustard	1	348	348	394	394	447	447	622	622
	Tathlina	6	245 - 589	373 ± 132	275 - 723	439 ± 172	338 - 1064	604 ± 293	507 - 1733	963 ± 512
	Trout	6	160 - 372	263 ± 69	175 - 447	307 ± 88	204 - 734	480 ± 187	297 - 1230	766 ± 344
	Total	**35**	**148 - 589**	**262 ± 89**	**164 - 723**	**301 ± 112**	**170 - 1064**	**386 ± 195**	**253 - 1733**	**581 ± 339**
Longnose Sucker	Kakisa	7	175 - 316	243 ± 46	195 - 369	275 ± 55	237 - 485	335 ± 84	297 - 696	470 ± 138
	McGill	4	148 - 291	203 ± 62	164 - 325	226 ± 69	170 - 364	241 ± 85	264 - 505	345 ± 108
	Mustard	1	348	348	394	394	447	447	622	622
	Tathlina	1	305	305	338	338	367	367	507	507
	Trout	6	160 - 372	263 ± 69	175 - 447	307 ± 88	204 - 734	480 ± 187	297 - 1230	766 ± 344
	Total	**19**	**148 - 372**	**250 ± 62**	**164 - 447**	**284 ± 76**	**170 - 734**	**369 ± 148**	**264 - 1230**	**547 ± 262**
White Sucker	Kakisa	7	178 - 340	247 ± 50	200 - 394	281 ± 60	221 - 510	331 ± 92	313 - 767	477 ± 146
	McGill	4	151 - 238	193 ± 36	166 - 270	216 ± 43	172 - 301	231 ± 53	253 - 436	334 ± 77
	Tathlina	5	245 - 589	386 ± 143	275 - 723	459 ± 184	338 - 1064	652 ± 301	515 - 1733	1055 ± 515
	Total	**16**	**151 - 589**	**277 ± 114**	**166 - 723**	**320 ± 144**	**172 - 1064**	**406 ± 243**	**253 - 1733**	**622 ± 418**

[1] Combining Longnose and White Sucker data sets.

Supplementary Table A2b. Species- and lake-specific fatty acid profiles for N-6/N-3 ratios of fish harvested in the Dehcho region, Northwest Territories, Canada (N=333).

Fish Species	Lake	N	N-6/N-3 Ratio	
			Range	Mean ± SD
Burbot	Mustard	5	0.65 - 0.8	0.75 ± 0.06
	Trout	9	0.45 - 0.6	0.50 ± 0.04
	Total	**14**	**0.45 - 0.80**	**0.59 ± 0.14**
Cisco	Ekali	5	0.30 - 0.41	0.36 ± 0.04
	Gargan	1	0.35	0.35
	Kakisa	8	0.24 - 0.35	0.3 ± 0.03
	Sanguez	1	0.34	0.34
	Trout	6	0.25 - 0.28	0.26 ± 0.01
	Total	**21**	**0.24 - 0.41**	**0.30 ± 0.05**
Lake Trout	Mustard	39	0.28 - 0.61	0.4 ± 0.08
	Trout	12	0.29 - 0.71	0.42 ± 0.14
	Total	**51**	**0.28 - 0.71**	**0.40 ± 0.10**
Lake Whitefish	Ekali	11	0.31 - 0.54	0.42 ± 0.08
	Gargan	16	0.31 - 0.64	0.46 ± 0.09
	Kakisa	10	0.28 - 0.57	0.38 ± 0.09

	McGill	9	0.29 - 0.66	0.45 ± 0.13
	Sanguez	3	0.32 - 0.53	0.41 ± 0.11
	Tathlina	9	0.24 - 0.53	0.40 ± 0.09
	Trout	10	0.22 - 0.55	0.34 ± 0.09
	Total	**68**	**0.22 - 0.66**	**0.41 ± 0.10**
Northern Pike	Ekali	17	0.3 - 0.49	0.37 ± 0.05
	Gargan	15	0.32 - 0.58	0.41 ± 0.07
	Kakisa	10	0.2 - 0.4	0.33 ± 0.06
	McGill	8	0.25 - 0.43	0.33 ± 0.06
	Mustard	5	0.36 - 0.61	0.46 ± 0.12
	Sanguez	10	0.27 - 0.44	0.36 ± 0.05
	Tathlina	10	0.29 - 0.57	0.4 ± 0.08
	Trout	10	0.2 - 0.36	0.28 ± 0.05
	Total	**85**	**0.20 - 0.61**	**0.37 ± 0.08**
Walleye	Ekali	17	0.30 - 0.48	0.37 ± 0.05
	Kakisa	8	0.31 - 0.44	0.36 ± 0.04
	McGill	7	0.36 - 0.42	0.38 ± 0.02
	Sanguez	7	0.32 - 0.44	0.36 ± 0.05
	Tathlina	9	0.36 - 0.62	0.48 ± 0.08
	Trout	11	0.21 - 0.35	0.27 ± 0.05
	Total	**59**	**0.21 - 0.62**	**0.37 ± 0.08**
Sucker[1]	Kakisa	14	0.25 - 0.53	0.41 ± 0.08
	McGill	8	0.39 - 0.55	0.44 ± 0.05
	Mustard	1	0.39	0.39
	Tathlina	6	0.38 - 0.68	0.56 ± 0.11
	Trout	6	0.46 - 0.73	0.56 ± 0.11
	Total	**35**	**0.25 - 0.73**	**0.47 ± 0.11**
Longnose Sucker	Kakisa	7	0.25 - 0.53	0.39 ± 0.1
	McGill	4	0.39 - 0.55	0.45 ± 0.07
	Mustard	1	0.39	0.39
	Tathlina	1	0.38	0.38
	Trout	6	0.46 - 0.73	0.56 ± 0.11
	Total	**19**	**0.25 - 0.73**	**0.46 ± 0.12**
White Sucker	Kakisa	7	0.39 - 0.5	0.43 ± 0.04
	McGill	4	0.40 - 0.47	0.44 ± 0.03
	Tathlina	5	0.51 - 0.68	0.6 ± 0.08
	Total	**16**	**0.39 - 0.68**	**0.49 ± 0.09**

Supplementary Table A3. Species- and lake-specific fatty acid profile for total omega-3 fatty acids of fish harvested in the Dehcho region, Northwest Territories, Canada (N=333).

Fish Species	Lake	N	Total fatty acids (mg/100g)	
			Range	Mean ± SD
Burbot	Mustard Lake	5	374 - 489	416 ± 47
	Trout Lake	9	236 - 372	311 ± 42
	Total	**14**	**236 - 489**	**348 ± 67**
Cisco	Ekali Lake	5	535 - 1649	1022 ± 454
	Gargan Lake	1	1180	1180
	Kakisa Lake	8	510 - 2400	1022 ± 588
	Sanguez Lake	1	1107	1107
	Trout Lake	6	806 - 1528	1043 ± 299
	Total	**21**	**510 - 2400**	**1039 ± 431**
Lake Trout	Mustard Lake	39	420 - 4203	1261 ± 921
	Trout Lake	12	700 - 13872	5650 ± 4041
	Total	**51**	**420 - 13872**	**2294 ± 2788**
Lake Whitefish	Ekali Lake	11	653 - 3816	1664 ± 1042
	Gargan Lake	16	705 - 2622	1412 ± 585
	Kakisa Lake	10	591 - 3752	2002 ± 1161
	McGill Lake	9	496 - 2119	1280 ± 655
	Sanguez Lake	3	1260 - 8727	4272 ± 3937
	Tathlina Lake	9	635 - 1787	1225 ± 356
	Trout Lake	10	612 - 2717	1059 ± 713
	Total	**68**	**496 - 8727**	**1572 ± 1202**
Northern Pike	Ekali Lake	17	388 - 2150	589 ± 406
	Gargan Lake	15	332 - 1156	462 ± 198
	Kakisa Lake	10	378 - 768	536 ± 126
	McGill Lake	8	317 - 656	486 ± 129
	Mustard Lake	5	544 - 760	622 ± 86
	Sanguez Lake	10	353 - 2205	632 ± 558
	Tathlina Lake	10	286 - 986	450 ± 200
	Trout Lake	10	449 - 1240	652 ± 267
	Total	**85**	**286 - 2205**	**549 ± 304**
Walleye	Ekali Lake	17	408 - 2325	802 ± 588
	Kakisa Lake	8	452 - 601	529 ± 56
	McGill Lake	7	412 - 987	541 ± 199
	Sanguez Lake	7	429 - 2030	834 ± 582
	Tathlina Lake	9	430 - 1151	609 ± 219
	Trout Lake	11	440 - 732	579 ± 84
	Total	**59**	**408 - 2325**	**667 ± 398**
Sucker[1]	Kakisa Lake	14	601 - 1969	1129 ± 465

	McGill Lake	8	444 - 1013	659 ± 216
	Mustard Lake	1	1445	1445
	Tathlina Lake	6	1169 - 5004	2685 ± 1621
	Trout Lake	6	685 - 4085	2474 ± 1332
	Total	**35**	**444 - 5004**	**1528 ± 1174**
Longnose Sucker	Kakisa Lake	7	616 - 1969	1140 ± 513
	McGill Lake	4	491 - 1013	651 ± 243
	Mustard Lake	1	1445	1445
	Tathlina Lake	1	1235	1235
	Trout Lake	6	685 - 4085	2474 ± 1332
	Total	**19**	**491 - 4085**	**1479 ± 1059**
White Sucker	Kakisa Lake	7	601 - 1948	1119 ± 453
	McGill Lake	4	444 - 971	666 ± 222
	Tathlina Lake	5	1169 - 5004	2975 ± 1629
	Total	**16**	**444 - 5004**	**1586 ± 1331**

[1] Combining Longnose and White Sucker data sets.

Supplementary Table A4. Full fatty acid profiles for fish species harvested in the Dehcho region, Northwest Territories, Canada (2013, 2014, 2015). Values are presented as mean ± standard deviation, in mg/100g.

Fatty Acid	Burbot (n=14)	Cisco (n=21)	Lake Trout (n=51)	Lake Whitefish (n=68)	Northern Pike (n=85)	Walleye (n=59)	Sucker[1] (n=35)	Longnose Sucker (n=19)	White Sucker (n=16)
C 10:0	0.06 ± 0.05	0.23 ± 0.29	0.36 ± 0.46	0.25 ± 0.24	0.23 ± 0.29	0.3 ± 0.5	0.17 ± 0.13	0.11 ± 0.08	0.24 ± 0.14
C 12:0	0.27 ± 0.14	1.5 ± 1.09	1.94 ± 2.79	4.21 ± 6.85	0.71 ± 0.85	0.82 ± 1.15	1.97 ± 3.11	1.69 ± 2.03	2.3 ± 4.1
C 14:0	2.63 ± 0.72	40.8 ± 32.7	57.5 ± 83.1	32 ± 40.4	6.71 ± 6.02	8.76 ± 7.42	37.8 ± 52.5	45.3 ± 61.7	28.8 ± 38.8
C 16:0	82.5 ± 11.8	217 ± 82.7	387 ± 461	310 ± 202	113 ± 73	155 ± 94.3	259 ± 166	267 ± 171	251 ± 165
C 17:0	1.91 ± 0.26	10.1 ± 6.43	14.2 ± 19.9	11.8 ± 18	2.52 ± 1.77	3.91 ± 2.84	8.85 ± 6.65	8.51 ± 6.38	9.25 ± 7.16
C 18:0	29.9 ± 3.34	69.7 ± 36.5	115 ± 126	78.1 ± 49	49.3 ± 54.5	66.4 ± 76.6	68.5 ± 28.8	71.1 ± 30.6	65.4 ± 27.1
C 20:0	0.54 ± 0.18	2.89 ± 1.59	3.9 ± 5.71	3.39 ± 3.41	1.18 ± 1.29	2.02 ± 2.53	3.33 ± 2.49	3.16 ± 2.26	3.53 ± 2.79
C 22:0	0.31 ± 0.16	1.81 ± 1.24	1.51 ± 2.44	2.16 ± 2.19	0.57 ± 0.69	1.19 ± 1.62	1.49 ± 0.52	1.33 ± 0.46	1.68 ± 0.54
C 24:0	0.29 ± 0.14	1.05 ± 0.77	0.9 ± 0.96	1.09 ± 0.62	0.8 ± 0.6	0.99 ± 1.03	0.95 ± 0.35	0.79 ± 0.3	1.14 ± 0.3
Total SFAs	**118 ± 14.5**	**346 ± 144**	**582 ± 696**	**443 ± 310**	**175 ± 132**	**239 ± 175**	**382 ± 255**	**399 ± 270**	**363 ± 243**
C 12:1	0.07 ± 0.09	0.61 ± 0.61	1.08 ± 0.99	0.86 ± 0.89	0.21 ± 0.34	0.18 ± 0.24	0.83 ± 0.78	0.82 ± 0.76	0.84 ± 0.83
C 14:1	0.1 ± 0.15	1.65 ± 1.82	2.86 ± 3.66	1.65 ± 2.13	0.33 ± 0.52	0.4 ± 0.63	2.49 ± 3.6	2.36 ± 3.11	2.64 ± 4.21
C 16:1	5.6 ± 3.11	69.1 ± 53.9	213 ± 284	161 ± 157	14.1 ± 17.2	22.1 ± 21.2	261 ± 303	256 ± 300	267 ± 316
C 18:1n-7	13.4 ± 6.1	53.4 ± 31.6	122 ± 164	93.4 ± 82.9	14.4 ± 10.1	21.9 ± 15.1	111 ± 96.1	102 ± 81.9	121 ± 112
C 18:1n-9	27.7 ± 6.86	101 ± 52.3	424 ± 609	276 ± 280	48 ± 30.2	61.1 ± 48.9	178 ± 186	160 ± 143	198 ± 231
C 20:1n-9	1.14 ± 0.4	3.56 ± 2.11	20 ± 26.7	14.2 ± 16.4	1.26 ± 0.97	1.97 ± 2.19	8.09 ± 7.88	8.76 ± 7.59	7.31 ± 8.39
C 22:1n-9	0.52 ± 0.27	2.24 ± 1.23	3.59 ± 4.13	3.47 ± 2.97	0.95 ± 0.72	1.37 ± 1.15	1.74 ± 0.87	1.49 ± 0.57	2.05 ± 1.08
C 24:1n-9	4.4 ± 1.71	4.57 ± 1.76	9.46 ± 10.2	5.59 ± 4.23	3.52 ± 1.85	6.79 ± 4.59	1.79 ± 0.59	1.98 ± 0.68	1.56 ± 0.38

Total MUFAs	**52.9 ± 17.8**	**236 ± 140**	**796 ± 1089**	**556 ± 534**	**82.8 ± 56.4**	**116 ± 88**	**564 ± 592**	**533 ± 533**	**601 ± 672**
C 18:2n-6	4.88 ± 1.46	35.9 ± 20.8	83.4 ± 107	55.5 ± 67.3	14.7 ± 9.33	13.2 ± 10.4	77.6 ± 89	84.6 ± 99.9	69.2 ± 76.5
C 18:3n-6	0.6 ± 0.28	2.99 ± 2.11	4.62 ± 5.4	4.98 ± 5.04	0.95 ± 0.95	1.26 ± 1.12	6.91 ± 10.9	4.74 ± 5.38	9.49 ± 14.9
C 20:2n-6	1.45 ± 0.89	3.52 ± 2.19	15.6 ± 19.5	8.4 ± 11.4	2.56 ± 1.88	2.06 ± 2.17	5.95 ± 4.97	5.28 ± 3.28	6.75 ± 6.47
C 20:3n-6	0.94 ± 0.25	2.9 ± 1.27	11.1 ± 11.8	5.09 ± 3.73	1.35 ± 0.98	1.55 ± 1.24	7.21 ± 5.89	7.29 ± 5.78	7.12 ± 6.21
C 20:4n-6	44.1 ± 16.8	39 ± 14	85.3 ± 54	71 ± 34	41.6 ± 19.9	44.9 ± 23.6	81.1 ± 48.3	63.6 ± 18.5	102 ± 63.4
C 22:2n-6	0.34 ± 0.12	1.26 ± 0.89	2.76 ± 4.59	1.87 ± 2.14	0.96 ± 0.89	1.06 ± 1.08	0.87 ± 0.61	0.86 ± 0.69	0.88 ± 0.51
C 22:4n-6	1.9 ± 1.14	4.31 ± 2.25	19.1 ± 20	8.77 ± 7.6	2.41 ± 1.58	3.65 ± 2.82	5.44 ± 4.94	3.6 ± 1.91	7.62 ± 6.45
C 22:5n-6	11.9 ± 4.6	17.8 ± 6.99	32.3 ± 40.8	16.2 ± 15.5	12.1 ± 8.78	15 ± 11.9	10.3 ± 6.12	8.48 ± 3.23	12.4 ± 7.97
Total N-6s	**66.2 ± 24.6**	**108 ± 46**	**254 ± 256**	**172 ± 139**	**76.7 ± 37.6**	**82.6 ± 47.2**	**195 ± 147**	**178 ± 119**	**215 ± 176**
C 18:3n-3	2.63 ± 0.77	46.5 ± 30	76.8 ± 124	47.6 ± 53.4	8.51 ± 7.85	8.78 ± 7.92	56.8 ± 63.4	61.1 ± 69.1	51.7 ± 57.9
C 18:4n-3	1.08 ± 0.3	25.1 ± 19.1	25.5 ± 42.4	18.1 ± 34.1	3.15 ± 3.81	3.66 ± 2.94	15.1 ± 26.2	9.36 ± 9.65	22 ± 36.7
C 20:3n-3	0.92 ± 0.14	4.63 ± 2.52	12.8 ± 25.5	5.78 ± 7.32	1.6 ± 1.41	1.94 ± 2.03	4.68 ± 3.19	4.81 ± 2.89	4.53 ± 3.6
C 20:4n-3	2.26 ± 0.51	15 ± 8.79	41.2 ± 82.2	9.77 ± 16.1	3.61 ± 3.61	4.31 ± 5.55	8.8 ± 8.13	9.6 ± 8.47	7.85 ± 7.86
C 20:5n-3	24.6 ± 7.37	68.5 ± 27.4	110 ± 101	93.4 ± 54.8	35.3 ± 16.4	36.7 ± 20.1	93 ± 61.2	78.8 ± 35.2	110 ± 80.2
C 22:5n-3	9.37 ± 3.61	24 ± 10.4	81 ± 91.9	31.6 ± 22.2	15.9 ± 8.67	16.5 ± 11.2	38.6 ± 23.7	34.5 ± 15.4	43.4 ± 30.8
C 22:6n-3	69.8 ± 12.3	167 ± 40.6	314 ± 333	195 ± 72.6	146 ± 73.6	157 ± 99	169 ± 38.8	171 ± 41.9	167 ± 36.1
Total omega-3 PUFAs	**111 ± 22**	**351 ± 123**	**662 ± 788**	**401 ± 248**	**214 ± 107**	**229 ± 137**	**386 ± 195**	**369 ± 148**	**406 ± 243**
Total PUFAs	**177 ± 44.2**	**458 ± 167**	**916 ± 1036**	**573 ± 384**	**291 ± 142**	**312 ± 182**	**581 ± 339**	**547 ± 262**	**622 ± 418**
Total HUFAs	**166 ± 41.6**	**344 ± 99.6**	**713 ± 762**	**437 ± 218**	**260 ± 126**	**283 ± 166**	**419 ± 180**	**382 ± 103**	**463 ± 238**
EPA+DHA	**94.4 ± 18.5**	**235 ± 61.3**	**424 ± 428**	**288 ± 122**	**181 ± 88.3**	**194 ± 117**	**262 ± 89.4**	**250 ± 62.5**	**277 ± 114**
EPA+DHA+DPA	**104 ± 21.6**	**259 ± 70.6**	**505 ± 517**	**320 ± 142**	**197 ± 96**	**211 ± 126**	**301 ± 112**	**284 ± 75.7**	**320 ± 144**
N-6/N-3 Ratio	**0.59 ± 0.14**	**0.3 ± 0.05**	**0.4 ± 0.1**	**0.41 ± 0.1**	**0.37 ± 0.08**	**0.37 ± 0.08**	**0.47 ± 0.11**	**0.46 ± 0.12**	**0.49 ± 0.09**
Total Fatty Acids	**348 ± 66.8**	**1039 ± 431**	**2294 ± 2788**	**1572 ± 1202**	**549 ± 304**	**667 ± 398**	**1528 ± 1174**	**1479 ± 1059**	**1586 ± 1331**

[1] Combining Longnose and White Sucker data sets.

Supplementary Table A5. Spearman rank coefficients for mercury vs. total omega-3 FAs, mercury vs. total polyunsaturated fatty acids, and mercury vs. EPA+DHA, by species, by lake for fish harvested from lakes of the Dehcho region, Northwest Territories, Canada (N=333).

Fish Species	Lake	N	Hg vs. EPA+DHA	Hg vs. EPA+DHA+DPA	Hg vs. *n*-3 FAs	Hg vs. PUFAs
Burbot	Mustard Lake	5	-0.300	-0.300	-0.600	-0.500
	Trout Lake	9	-0.350	-0.350	-0.317	-0.317
	Total	**14**	**-0.618***	**-0.666***	**-0.670***	**-0.798***
Cisco	Ekali Lake	5	-0.200	-0.100	-0.300	-0.300
	Gargan Lake	1	N/A	N/A	N/A	N/A
	Kakisa Lake	8	-0.548	-0.548	-0.714*	-0.714*
	Sanguez Lake	1	N/A	N/A	N/A	N/A
	Trout Lake	6	0.600	0.600	0.543	0.543
	Total	**21**	**-0.334**	**-0.325**	**-0.278**	**-0.200**
Lake Trout	Mustard Lake	39	-0.513*	-0.596**	-0.631**	-0.615**
	Trout Lake	12	-0.951**	-0.951**	-0.937**	-0.951**
	Total	**51**	**-0.182**	**-0.226**	**-0.241**	**-0.212**
Lake Whitefish	Ekali Lake	11	0.118	0.209	0.209	0.209
	Gargan Lake	16	-0.436	-0.407	-0.501*	-0.372
	Kakisa Lake	10	0.079	0.079	0.006	0.006
	McGill Lake	9	-0.151	-0.034	-0.067	-0.067
	Sanguez Lake	3	-0.500	-0.500	-0.500	-0.500
	Tathlina Lake	9	-0.167	-0.234	-0.042	-0.084
	Trout Lake	10	-0.103	-0.357	-0.333	-0.152
	Total	**68**	**-0.110**	**-0.060**	**-0.058**	**0.033**
Northern Pike	Ekali Lake	17	-0.314	-0.316	-0.243	-0.363
	Gargan Lake	15	-0.593*	-0.636*	-0.602*	-0.525*
	Kakisa Lake	10	-0.442	-0.467	-0.467	-0.224
	McGill Lake	8	-0.738*	-0.809*	-0.738*	-0.833*
	Mustard Lake	5	0.100	0.100	0.100	0.600
	Sanguez Lake	10	-0.188	-0.236	-0.309	-0.236
	Tathlina Lake	10	0.018	0.018	-0.055	-0.018
	Trout Lake	10	-0.067	-0.067	-0.067	-0.067
	Total	**85**	**-0.506****	**-0.521****	**-0.479****	**-0.439****
Walleye	Ekali Lake	17	-0.380	-0.382	-0.400	-0.353
	Kakisa Lake	8	-0.786*	-0.691	-0.643	-0.429
	McGill Lake	7	0.143	-0.071	0.071	0.107
	Sanguez Lake	7	-0.286	-0.464	-0.500	-0.500
	Tathlina Lake	9	-0.450	-0.467	-0.467	-0.500
	Trout Lake	11	-0.482	-0.436	-0.436	-0.527
	Total	**59**	**-0.480****	**-0.452***	**-0.446***	**-0.397***

Sucker[1]	Kakisa Lake	14	0.697*	0.736*	0.776*	0.714*
	McGill Lake	8	0.122	0.122	0.122	0.268
	Mustard Lake	1	N/A	N/A	N/A	N/A
	Tathlina Lake	6	0.493	0.493	0.638	0.580
	Trout Lake	6	-0.086	-0.143	-0.429	-0.314
	Total	**35**	**0.275**	**0.276**	**0.134**	**0.164**
Longnose Sucker	Kakisa Lake	7	0.714	0.750	0.750	0.714
	McGill Lake	4	-0.200	-0.200	-0.200	-0.200
	Mustard Lake	1	N/A	N/A	N/A	N/A
	Tathlina Lake	1	N/A	N/A	N/A	N/A
	Trout Lake	6	-0.086	-0.143	-0.429	-0.314
	Total	**19**	**0.147**	**0.147**	**-0.086**	**-0.023**
White Sucker	Kakisa Lake	7	0.821*	0.821*	0.893*	0.893*
	McGill Lake	4	0.316	0.316	0.316	0.316
	Tathlina Lake	5	0.359	0.359	0.359	0.359
	Total	**16**	**0.561***	**0.561***	**0.543***	**0.541***

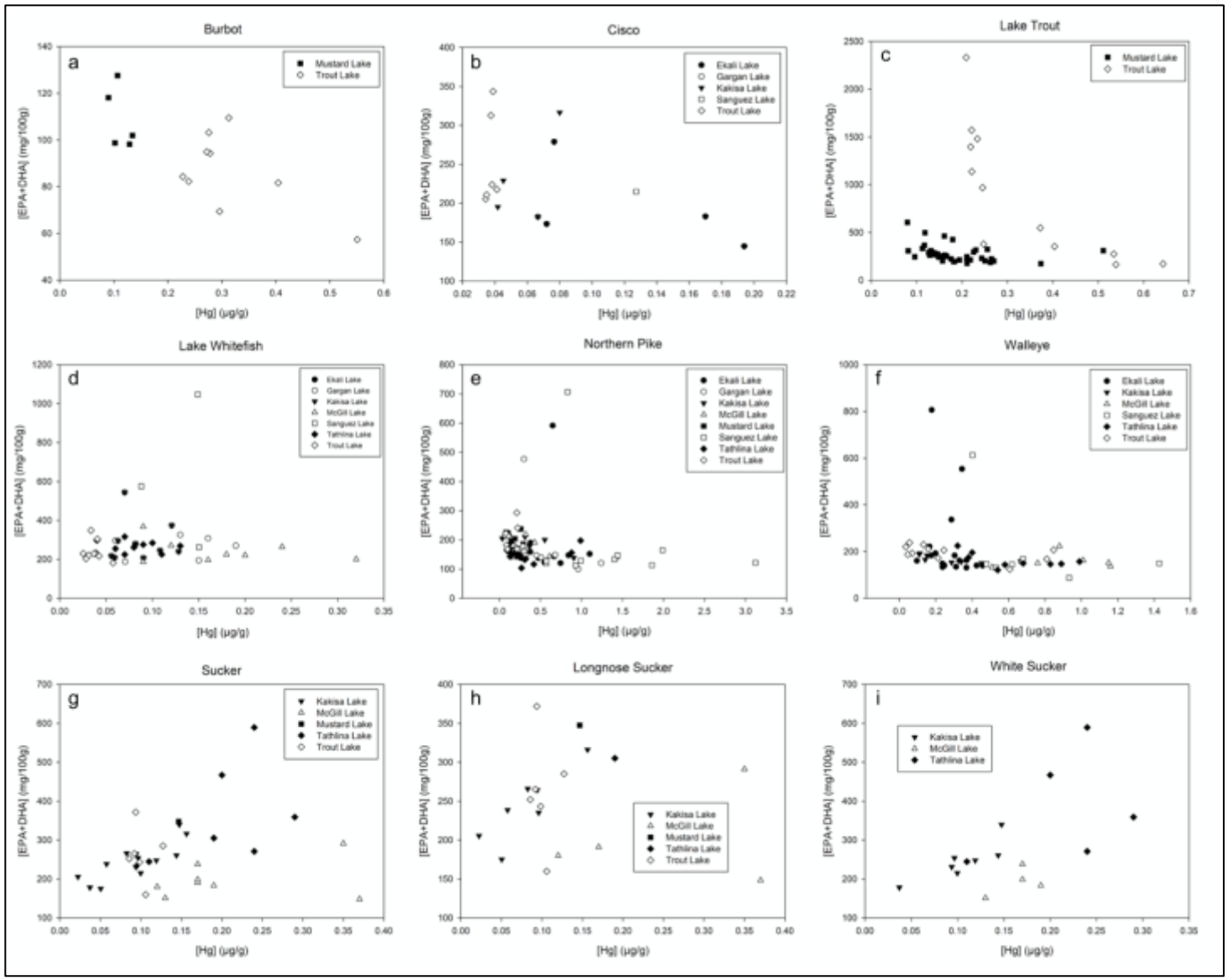
[1] Combining Longnose and White Sucker data sets.
* - Statistically Significant where $p<.05$.
** - Statistically significant where $p<.001$.

Supplementary Table A6. Fatty acid:mercury ratios (mean ± standard deviation in mg:µg) for fish species harvested in freshwater lakes of the Dehcho region, Northwest Territories, Canada.

Fish Species	Lake	N=333	DHA:Hg	EPA+DHA:Hg	EPA+DHA+DPA: Hg	Total *n*-3s:Hg	Total PUFAs:Hg
			15.38	**19.23**	**-**	**38.46**	**-**
Burbot	Mustard Lake	5	7.04 ± 1.73	10 ± 2.51	11.26 ± 2.89	11.89 ± 3.09	20.76 ± 5.2
	Trout Lake	9	2.26 ± 0.71	2.97 ± 0.94	3.21 ± 1.02	3.45 ± 1.08	5.13 ± 1.57
	Overall	**14**	**3.97 ± 2.62**	**5.48 ± 3.83**	**6.08 ± 4.38**	**6.46 ± 4.62**	**10.71 ± 8.38**
Cisco	Ekali Lake	5	15.22 ± 8.36	21.22 ± 12	23.31 ± 13.33	33.14 ± 22.66	45.18 ± 31.36
	Gargan Lake	1	30.97	39.56	42.96	57.36	77.65
	Kakisa Lake	8	39.14 ± 10.61	57.78 ± 18.77	64.27 ± 22.37	84.79 ± 41.18	110.94 ± 56.85
	Sanguez Lake	1	11.04	16.89	18.69	28.93	38.63
	Trout Lake	6	49.05 ± 9.4	67.17 ± 14.8	73.6 ± 16.7	99.73 ± 25.84	125.51 ± 33.26
	Overall	**21**	**34.55 ± 16.39**	**48.94 ± 24.2**	**54.00 ± 27.24**	**72.80 ± 40.49**	**94.42 ± 52.72**
Lake Trout	Mustard Lake	39	12.67 ± 7.95	18.34 ± 12.93	21.8 ± 16.2	26.75 ± 23.12	38.17 ± 34.28
	Trout Lake	12	29.15 ± 26.94	37.55 ± 34.99	45.11 ± 42.01	64.55 ± 63.1	86.46 ± 81.88
	Overall	**51**	**16.54 ± 16.05**	**22.86 ± 21.55**	**27.29 ± 26.22**	**35.64 ± 39.3**	**49.54 ± 52.88**
Lake Whitefish	Ekali Lake	11	25.1 ± 10.03	35.37 ± 16.27	38.94 ± 18.36	49.52 ± 28.29	71.27 ± 44.04
	Gargan Lake	16	19.91 ± 12.05	28.37 ± 17.07	31.31 ± 18.74	37.41 ± 23.41	54.29 ± 34.05
	Kakisa Lake	10	57.67 ± 26.36	90.82 ± 47.33	101.78 ± 54.29	132.66 ± 81.75	184.47 ± 118.55
	McGill Lake	9	11.46 ± 7.25	17.58 ± 10.34	19.58 ± 11.37	22.66 ± 13.18	32.85 ± 18.51

	Sanguez Lake	3	33.98 ± 19.05	51.08 ± 29.22	57.33 ± 33.52	87.3 ± 59.13	125.37 ± 90.66
	Tathlina Lake	9	25.58 ± 13.48	36.35 ± 16.54	39.78 ± 18.16	47.44 ± 21.06	66.93 ± 30.64
	Trout Lake	10	44.89 ± 9.89	67.71 ± 20.24	74.45 ± 23.89	89.14 ± 36.41	120.97 ± 58.34
	Overall	**68**	**30.23 ± 20.44**	**45.10 ± 33.4**	**49.97 ± 37.73**	**62.56 ± 52.78**	**87.96 ± 75.44**
Northern Pike	Ekali Lake	17	4.69 ± 3.1	5.85 ± 3.9	6.27 ± 4.15	6.73 ± 4.42	9.23 ± 6.04
	Gargan Lake	15	5.27 ± 3.46	6.5 ± 4.25	7.08 ± 4.64	7.4 ± 4.83	10.22 ± 6.46
	Kakisa Lake	10	11.32 ± 13.29	14.5 ± 16.49	16.3 ± 18.33	17.75 ± 19.87	23.05 ± 25.25
	McGill Lake	8	5.31 ± 4.41	6.9 ± 6.13	7.63 ± 6.89	8.45 ± 7.83	11.2 ± 10.43
	Mustard Lake	5	13.16 ± 6.47	16.45 ± 7.83	17.91 ± 8.57	18.73 ± 8.88	26.68 ± 11.26
	Sanguez Lake	10	1.89 ± 2.23	2.25 ± 2.64	2.4 ± 2.82	2.65 ± 3.1	3.52 ± 4.00
	Tathlina Lake	10	5.18 ± 3.72	6.50 ± 4.80	7.12 ± 5.29	7.49 ± 5.51	10.48 ± 7.79
	Trout Lake	10	13.55 ± 6.4	17.08 ± 8.09	18.52 ± 8.71	20.88 ± 9.37	26.56 ± 11.64
	Overall	**85**	**6.90 ± 6.91**	**8.68 ± 8.69**	**9.49 ± 9.59**	**10.29 ± 10.44**	**13.75 ± 13.44**
Walleye	Ekali Lake	17	8.27 ± 8.5	10.03 ± 10.12	10.73 ± 10.76	11.71 ± 11.51	15.88 ± 15.2
	Kakisa Lake	8	7.39 ± 4.87	9.21 ± 6.07	10.26 ± 6.72	10.96 ± 7.18	14.81 ± 9.57
	McGill Lake	7	1.5 ± 0.43	1.94 ± 0.58	2.14 ± 0.66	2.37 ± 0.8	3.27 ± 1.10
	Sanguez Lake	7	3.36 ± 4.37	3.94 ± 5.05	4.23 ± 5.35	4.58 ± 5.69	6.14 ± 7.45
	Tathlina Lake	9	2.47 ± 1.34	3.16 ± 1.9	3.47 ± 2.12	3.76 ± 2.40	5.59 ± 3.73
	Trout Lake	11	15.94 ± 14.83	20.54 ± 20.02	21.98 ± 21.42	23.75 ± 22.9	30.58 ± 30.04
	Overall	**59**	**7.31 ± 9.32**	**9.15 ± 12.04**	**9.87 ± 12.87**	**10.68 ± 13.8**	**14.26 ± 17.99**
Sucker[1]	Kakisa Lake	14	21.86 ± 13.26	32.57 ± 19.12	36.91 ± 22.05	43.39 ± 24.27	61.5 ± 35.93
	McGill Lake	8	8.12 ± 2.52	10.69 ± 3.45	11.94 ± 3.91	12.72 ± 4.19	18.27 ± 5.93
	Mustard Lake	1	17.51	23.69	26.88	30.50	42.37
	Tathlina Lake	6	10.27 ± 2.86	18.32 ± 5.82	21.42 ± 7.15	28.85 ± 11.18	45.71 ± 19.8
	Trout Lake	6	15.96 ± 3.45	26.72 ± 8.23	31.22 ± 10.52	49.34 ± 22.41	78.97 ± 40.99
	Total	**35**	**15.6 ± 10.29**	**23.87 ± 15.36**	**27.28 ± 17.75**	**34.54 ± 22.59**	**51.36 ± 35.33**
Longnose Sucker	Kakisa Lake	7	26.73 ± 16.62	39.05 ± 24.36	44.22 ± 28.35	52.56 ± 30.74	73.99 ± 46.5
	McGill Lake	4	7.47 ± 3.51	9.64 ± 4.65	10.76 ± 5.24	11.38 ± 5.42	16.23 ± 7.42
	Mustard Lake	1	17.51	23.69	26.88	30.50	42.37
	Tathlina Lake	1	12.75	16.06	17.77	19.32	26.69
	Trout Lake	6	15.96 ± 3.45	26.72 ± 8.23	31.22 ± 10.52	49.34 ± 22.41	78.97 ± 40.99
	Overall	**19**	**18.05 ± 12.43**	**26.94 ± 18.73**	**30.77 ± 21.75**	**39.96 ± 27.58**	**59.25 ± 43.55**
White Sucker	Kakisa Lake	7	16.99 ± 7.03	26.08 ± 10.03	29.59 ± 11.15	34.23 ± 11.65	49.01 ± 16.49
	McGill Lake	4	8.77 ± 1.2	11.75 ± 1.79	13.12 ± 2.12	14.06 ± 2.62	20.31 ± 3.97
	Tathlina Lake	5	9.77 ± 2.9	18.77 ± 6.39	22.15 ± 7.74	30.75 ± 11.36	49.52 ± 19.53
	Overall	**16**	**12.68 ± 6.15**	**20.21 ± 9.36**	**23.15 ± 10.64**	**28.10 ± 12.75**	**41.99 ± 19.52**

[1] Combining Longnose and White Sucker data sets.



Supplementary Figure A1. EPA+DHA vs. Total Mercury (HgT) concentrations from the muscle tissue samples of fish species harvested across lakes in the Dehcho during 2013, 2014, and 2015.

Appendix B – Supplementary Tables

Supplementary Table B1. Primary contributors to the variance of total DHA intake (g d^{-1}).

Input Variable	Contribution to Variance (%)	Rank Correlation
LKWH_IR	24%	0.47
LKTR_% Consuming	14%	0.36
LKWH_% Consuming	6.2%	0.24
WALL_% Consuming	5.8%	0.23
LKTR_IR	5.4%	0.22
NRPK_% Consuming	5.3%	0.22
* LKWH_[DHA]	3.6%	0.18
* LKWH_[EPA+DHA]	2.6%	0.15
NRPK_IR	2.5%	0.15
* LKTR_[DHA]	2.2%	0.14

* indicates correlated assumptions (Crystal Ball outlines that therefore sensitivity data may be misleading)

Supplementary Table B2. Primary contributors to the variance of total EPA+DHA intake (g d^{-1}).

Input Variable	Contribution to Variance (%)	Rank Correlation
LKWH_IR	26%	0.50
LKTR_% Consuming	12%	0.34
LKWH_% Consuming	6.8%	0.26
LKTR_IR	4.9%	0.22
WALL_% Consuming	4.3%	0.20
NRPK_% Consuming	3.9%	0.19
* LKWH_[EPA+DHA]	3.8%	0.19
* LKWH_[DHA]	3.7%	0.19
* LKWH_[EPA+DHA+DPA]	3.6%	0.19
* LKWH_[N-3]	3.3%	0.18

* indicates correlated assumptions (Crystal Ball outlines that therefore sensitivity data may be misleading)

Supplementary Table B3. Primary contributors to the variance of total omega-3 intake (g d^{-1}).

Input Variable	Contribution to Variance (%)	Rank Correlation
LKWH_IR	22%	0.48
LKTR_% Consuming	11%	0.35
LKWH_% Consuming	6.3%	0.26
* LKWH_[N-3]	6.0%	0.25
* LKWH_[EPA+DHA+DPA]	5.8%	0.25
* LKWH_[EPA+DHA]	5.7%	0.25
* LKWH_[PUFAs]	5.5%	0.24
* LKWH_[DHA]	4.6%	0.22
LKTR_IR	4.1%	0.21
WALL_% Consuming	2.9%	0.17

* indicates correlated assumptions (Crystal Ball outlines that therefore sensitivity data may be misleading)

Supplementary Table B4. Primary contributors to the variance of total PUFA intake (g d^{-1}).

Input Variable	Contribution to Variance (%)	Rank Correlation
LKWH_IR	21%	0.48
LKTR_% Consuming	11%	0.34
* LKWH_[PUFAs]	6.7%	0.27
* LKWH_[N-3]	6.6%	0.27
* LKWH_[EPA+DHA+DPA]	6.3%	0.26
LKWH_% Consuming	6.3%	0.26
* LKWH_[EPA+DHA]	6.0%	0.25
* LKWH_[DHA]	4.4%	0.22
LKTR_IR	4.0%	0.21
SUCK_% Consuming	3.0%	0.18

* indicates correlated assumptions (Crystal Ball outlines that therefore sensitivity data may be misleading

Supplementary Table B5. Primary contributors to the variance of methylmercury intake (μg kg^{-1} d^{-1}).

Input Variable	Contribution to Variance (%)	Rank Corr.
NRPK_% Consuming	22%	0.40
WALL_% Consuming	21%	0.40
* NRPK_[HgT]	7.4%	0.24
General Population BW	5.9%	-0.21
LKTR_% Consuming	5.2%	0.20
NRPK_IR	5.1%	0.20
LKWH_IR	3.8%	0.17
WALL_IR	3.3%	0.16
LKTR_IR	2.7%	0.14
* WALL_[HgT]	2.5%	0.14

* Indicates correlated assumptions (Crystal Ball outlines that therefore sensitivity data may be misleading)